

# Approaches to the Total Synthesis of Calycotomine, a Widespread 1-Hydroxymethyl-Substituted Simple Tetrahydroisoquinoline

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**Abstract:** 1-Hydroxymethyl-substituted tetrahydroisoquinolines are scarce in nature; the widespread alkaloid calycotomine is its most prominent example. The different total syntheses of this natural product, used as test ground for the development of novel synthetic methodologies during the last forty years, and those of some structurally related precursors, are reviewed.

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**Key words:** natural products, total synthesis, alkaloids, cyclizations, calycotomine

## 1 Introduction

The isoquinoline alkaloids comprise a large group of compounds that are found in nature in a wide variety of plant families, and that have been isolated from soil and marine microorganisms as well.<sup>1</sup> These natural products display great structural diversity, with a substantial number of them being 1-substituted derivatives.

Despite the abundance of 1-substituted tetrahydroisoquinolines, the presence of an hydroxymethyl group as a substituent at position C-1 of the isoquinoline nucleus is uncommon among the simple naturally occurring tetrahydroisoquinolines.<sup>2</sup> Typical examples of the rare occurrence of this feature among the natural products isolated from higher plants include calycotomine (**1**),<sup>3</sup> hedycarine (**2**),<sup>4</sup> heterocarpine (**3**),<sup>5</sup> from *Ceratocarpus heterocarpus*, and deglucopterocercine (**4**),<sup>6</sup> its *N*-oxide (**5**), and its (–)-5β-*O*-glucopyranoside (glucopterocercine)<sup>7</sup> from *Pterocercus gaumeri*. Structurally related to these tetrahydroisoquinolines is the β-adrenergic receptor antagonist MY336-a (**6**),<sup>8a,b</sup> of fungal origin, which was isolated from the fermentation broth of *Streptomyces gabonae* KY2234 and which displays a second hydroxymethyl group at C-3 (Figure 1). Interestingly, 1-hydroxymethyl-

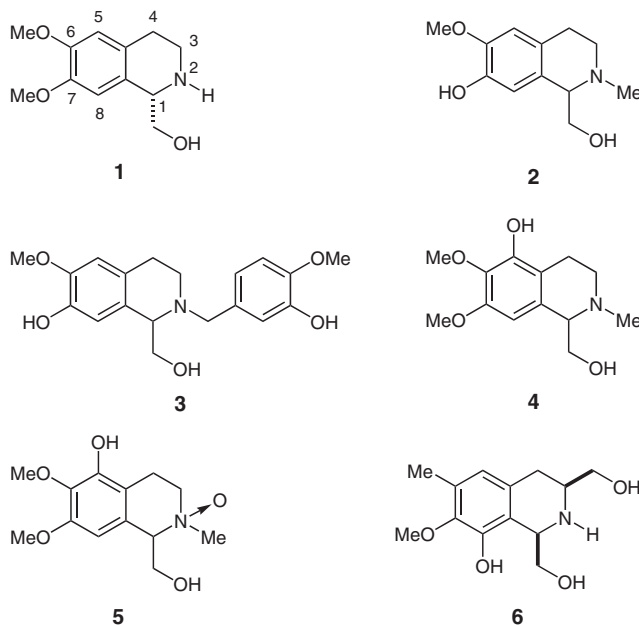


Figure 1

substituted simple isoquinolines have recently been isolated from *Haliclona* sp. marine sponges.<sup>8c</sup>

Other, more complex isoquinoline alkaloids, share the same structural feature.

Among the benzophenanthridines (Figure 2) are bocconoline (**7**) from *Macleaya cordata*,<sup>9a</sup> the root bark of *Zanthoxylum simulans*,<sup>9b–d</sup> *Bocconia cordata* Willd,<sup>9e,f</sup> and *Chelidonium japonicum*,<sup>10</sup> from which it was isolated together with 8-hydroxymethylsanguinarine (**8**), 8-hydroxymethylidihydronitidine (**9**)<sup>11</sup> and corynolamine (**10**).<sup>12</sup>

Solidaline (**11**),<sup>13</sup> isolated from *Corydalis solida*, (+)-malacitanine (**12**), accessed from *Ceratocarpus heterocarpus*,<sup>14</sup> and ziginlongine (**13**),<sup>15</sup> obtained from *Dactylocarpus torulosa*, are the only three examples of natural tetrahydroprotoberberine alkaloids carrying the hydroxymethyl feature attached to the C-1 position of a tetrahydroisoquinoline-based skeleton (Figure 3). These berberines are minor alkaloids in their source plants and the biosynthetic origin<sup>16</sup> of the hydroxymethyl group is still unknown; however, in the case of (+)-malacitanine, it probably comes from the in vivo addition of a one-carbon

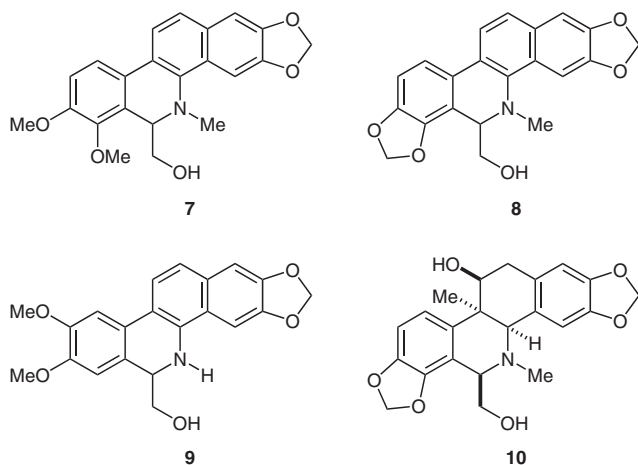


Figure 2

unit that has pyruvate or glyoxylate as two potential precursors.<sup>17</sup>

More complex isoquinoline alkaloids, such as quinocarcin (**14**),<sup>18a</sup> the related tetrazomine (**15**)<sup>18b</sup> produced by several *Streptomyces* species and the ecteinascidins, such as ecteinascidin 743 (**16**) from the marine tunicate *Ecteinascidia turbinata*,<sup>19</sup> also bear 1-hydroxymethyl substituents attached to isoquinoline moieties (Figure 4).

Calycotomine (**1**) is a simple tetrahydroisoquinoline alkaloid, isolated from different species of *Calycotome*, *Genista*, *Cistus* and *Acacia* (Fam. Fabaceae), among other sources. It was first isolated in 1944 by White from the Australian plant *Calycotome spinosa* Link.<sup>20</sup> as the optically active (*S*)-(+)-enantiomer. The natural product was also isolated in this optically active form from *Cystius proliferus*,<sup>21</sup> as well as from the aerial parts of *Genista anatolica* (0.009%)<sup>22</sup> and *Genista involucrata* (0.0043%).<sup>23</sup> In addition, calycotomine was obtained in non-specified enantiomeric form from *Acacia concinna*<sup>24</sup>

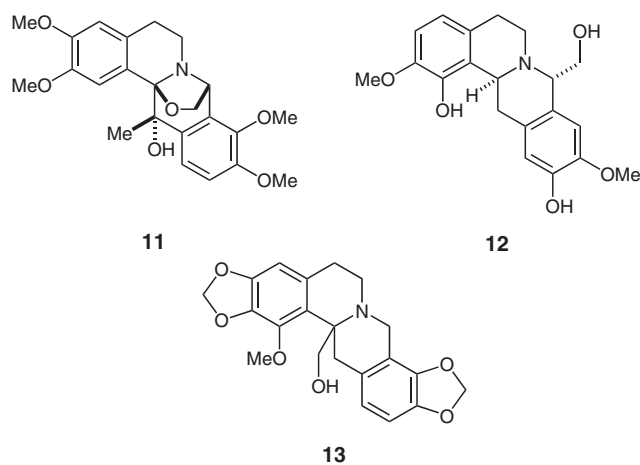


Figure 3

and other plants, such as *Genista burdurensis* (0.012%)<sup>25</sup> and *Genista sessifolia* grown in Turkey.<sup>26</sup>

Interestingly, calycotomine was recently found, together with its *N*-methyl-*O*-acetyl derivative, in the leaves and seeds of *Calycotome villosa* Link.,<sup>27a</sup> an erect shrub of up to two meters tall which grows in cold places of central Sardinia at 500–900 meters above the sea level and in the Tezzaka plateau of Morocco.<sup>27b</sup> The alkaloid is also present in the seeds of *Chamaesythus proliferus* sp. *proliferus* var. *palmensis* (Fabaceae), which has long been known to contain different alkaloids.<sup>28</sup> Since it is employed as forage in the Canary Islands and in New Zealand, concerns about toxicity have triggered analytical studies on the alkaloid composition of different *Chamaesythus proliferus* sub-species. After TLC and GC-MS analyses, it was concluded that sparteine is the major alkaloid in these plants, accounting for up to 90% of their total alkaloid content.<sup>29</sup>

## Biographical Sketch



**Teodoro Saúl Kaufman** was born in Moises Ville (Santa Fe, Argentina). He graduated as Biochemist (1982) and Pharmacist (1985) from the National University of Rosario (UNR, Argentina) and received his PhD in Organic Chemistry from the same University (1987), working with Professor Edmundo A. Rúveda in the synthesis of terpenes of geochemical interest. From 1987 to 1989, he was a postdoctoral fellow

in the laboratory of Prof. Robert D. Sindelar at The University of Mississippi (USA), working on the design and synthesis of analogs of the naturally occurring complement inhibitor K-76. In 1990, he became Assistant Research Scientist of the Argentine National Research Council (CONICET) and was appointed Assistant Professor at the UNR. He is now Associate Professor (UNR), Independent Research Sci-

entist of CONICET and Sub-Director of IQUIOS, the Institute of Synthetic Organic Chemistry (Rosario, Argentina). His main research interests include the development of novel synthetic methods, asymmetric synthesis and the synthesis of natural products and bioactive compounds. The work in his laboratory has been supported by ANP-CyT, CONICET, Fundación Antorchas, IFS and TWAS.

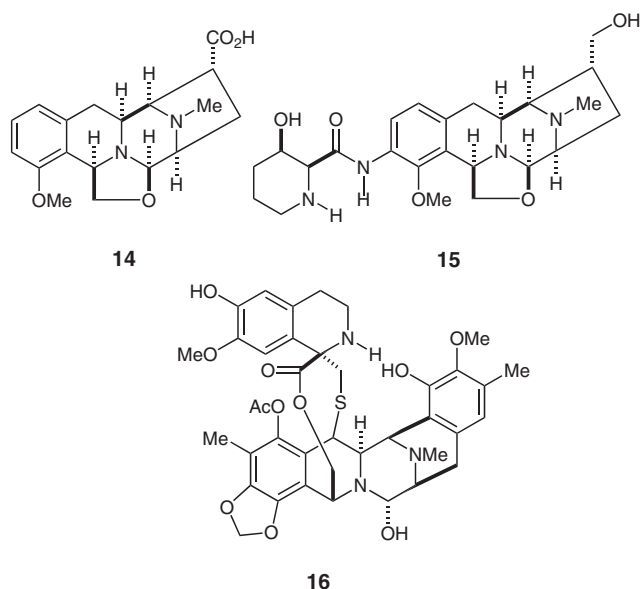
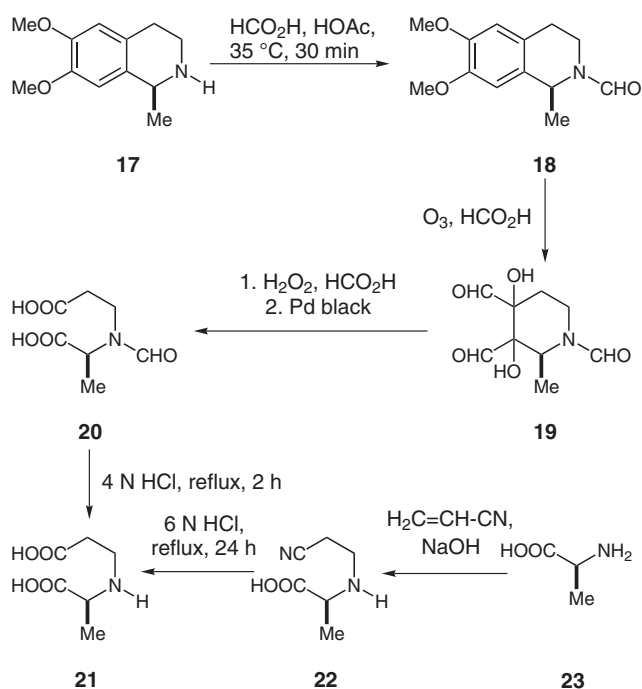


Figure 4

The absolute configuration of several 1-substituted tetrahydroisoquinolines, including that of calycotomine, has been deduced by chemical correlations, thanks to the seminal work of Battersby and Edwards,<sup>30a</sup> which allowed the unequivocal establishment of the absolute configuration of (*S*)-salsolidine (**17**). As shown in Scheme 1, this was based on the oxidation of (–)-*N*-formyl salsolidine (**18**) with ozone to give the triformyl intermediate **19**, which was cleaved with hydrogen peroxide in formic acid to diacid **20** which was then hydrolyzed under acidic conditions to furnish *N*-carboxyethyl-L-alanine (**21**). The latter was compared with an identical material produced by Michael addition of L-alanine **23** onto acrylonitrile, followed by acid hydrolysis of the resulting nitrile **22**.

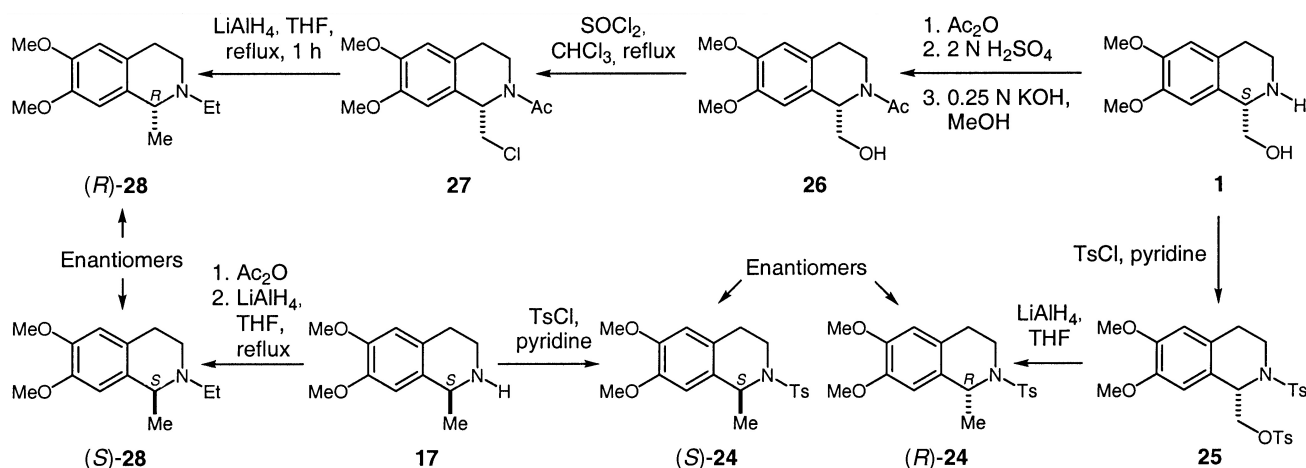
Once the absolute configuration of natural (*S*)-salsolidine (**17**) was established, sulfonamide (*S*)-**24** was prepared by sulfonamidation of the latter (Scheme 2) and compared with its enantiomer. (*R*)-**24** was synthesized by sulfonamidation of chiral calycotomine (**1**) followed by selective re-



Scheme 1

duction of a tosylate moiety in the resulting ditosylate **25** with lithium aluminum hydride in THF.<sup>30a</sup> X-ray diffraction data of (*R*)-**1** and (*S*)-**1**·HCl have been published.<sup>27b</sup>

In addition, *N*-ethylsalsolidine (*S*)-**28**, prepared by acetylation of salsolidine (**17**) followed by lithium aluminum hydride reduction of the resulting amide, was compared with its enantiomer, (*R*)-**28**. The *R* enantiomer was synthesized by selective *N*-acylation of calycotomine (**1**) followed by transformation of primary alcohol **26** into the related chloride **27** and a final lithium aluminum hydride reduction. Both comparisons between the enantiomer pairs of **24** and **28** revealed that the optically active form of the naturally occurring alkaloid has the (1*S*) absolute configuration. Interestingly, this is opposite to that of most of the known simple tetrahydroisoquinolines.



Scheme 2

Chemists' interest in the synthesis of tetrahydroisoquinolines is almost as old as the discovery of the isoquinoline ring system itself. Despite its apparent simplicity, the synthesis of the isoquinoline skeleton has been approached in several ways. Kametani, who also made contributions to the synthesis of calycotomine derivatives,<sup>31a</sup> has proposed that the approaches towards the synthesis of the isoquinoline framework can be categorized into 15 different methods.<sup>31b,c</sup> The first five types include strategies consisting of elaboration of the heterocyclic ring through the formation of one C–C or C–N bond (Figure 5).

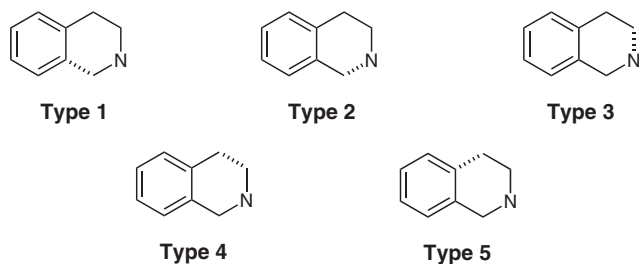


Figure 5

The first type involves a ring closure between the carbon atom which constitutes C-1 of the isoquinoline and the aromatic ring, while type two describes formation of the heterocycle by C–N bonding between C-1 and the nitrogen. Type 3 necessitates formation of the C–N bond between the nitrogen and the atom which will constitute C-3 in the resulting isoquinoline. Similarly, the fourth type involves joining of C-3 and C-4, and the fifth type is assigned to protocols in which the isoquinoline ring formation is concluded by the formation of a C–C bond between the aromatic moiety and the C-4 position. The literature records examples of all of the five types for the synthesis of different isoquinoline derivatives, including many nat-

ural products; however, synthetic protocols of types 1 (Bischler–Napieralski and Pictet–Spengler), 2 and 5 (Pomerantz–Fritsch and its modifications) are the most widely used for the elaboration of tetrahydroisoquinolines.

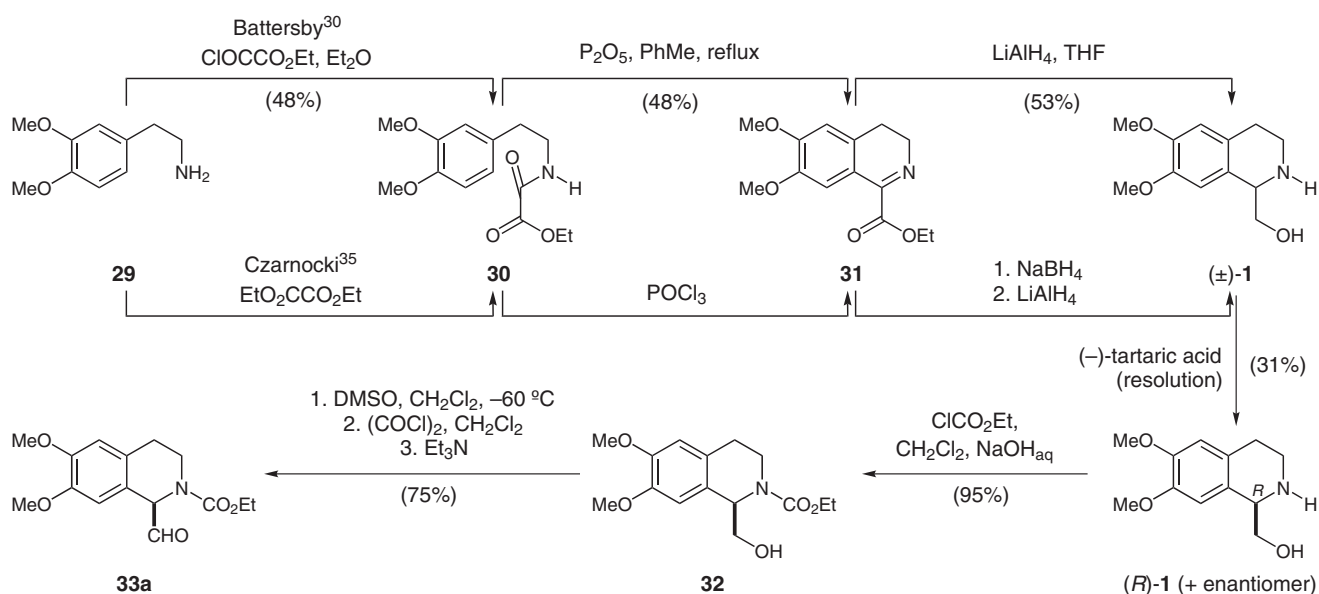
Most of the many syntheses of calycotomine described to date have been carried out by the classical and more commonly used isoquinoline forming reactions: Bischler–Napieralski, Pictet–Spengler and Pomerantz–Fritsch protocols, and some of their modern variations and modifications. Calycotomine has also been prepared starting from preformed isoquinolines, synthesized by any of the above methods. Other syntheses, employing less conventional approaches such as allylic amination (type 2 synthesis) and perhydroxazine ring opening (type 1 synthesis) have also been disclosed.

This review covers the synthetic approaches to calycotomine both in racemic and optically active forms; the preparation of known advanced precursors, derivatives and related compounds are also included. The syntheses will be discussed according to the synthetic strategy employed for gaining access to the target compounds.

## 2 Bischler–Napieralski Cyclization

The first attempts at the synthesis of calycotomine, in the 1940s, employed a Pictet–Spengler approach; however, these met with scarce success and many of them failed. In spite of the publication of other contemporary attempts,<sup>30b</sup> in 1959, Battersby and Edwards<sup>30c</sup> reported their Bischler–Napieralski strategy towards the natural product, as the first straightforward and synthetically efficient protocol for calycotomine (Scheme 3).

In this synthesis, homoveratrylamine **29** was reacted with ethoxalyl chloride and the resulting amide **30**<sup>32</sup> was cyclized with phosphorus pentoxide in refluxing toluene,



Scheme 3

giving 48% of 3,4-dihydroisoquinoline ester **31**,<sup>33</sup> after several cycles of partial cyclization and separation of the cyclized material from the starting amide. Both reducible groups were simultaneously attacked by lithium aluminum hydride in THF, furnishing the natural product in racemic form and in 53% yield. The thus synthesized racemic product was resolved employing *O,O*-di-*p*-toluyl tartrate.

Schneider and Schilken<sup>34a</sup> also synthesized ethyl 6,7-dimethoxy-3,4-dihydroisoquinoline-1-carboxylate (**31**); in addition, these authors prepared the oxazolidine and spiro-oxazolidine derivatives of calycotomine, while the group of Fülöp synthesized calycotomine thiocarbamides by reaction of the alkaloid with isothiocyanates.<sup>34b</sup>

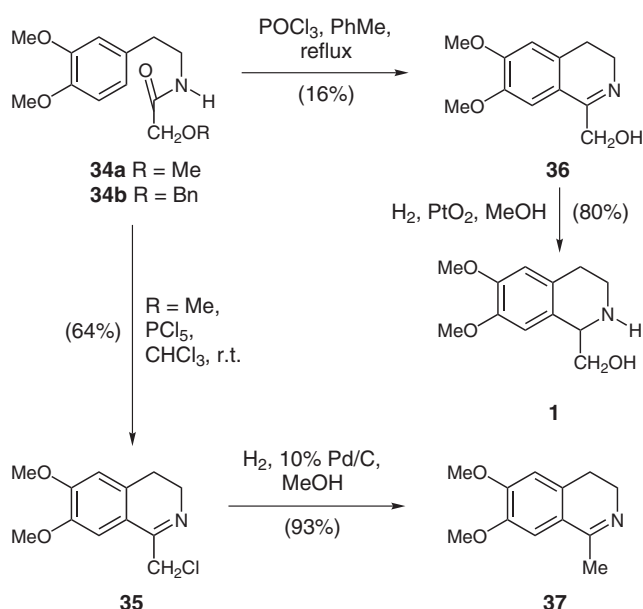
A path analogous to that of Battersby and Edwards was followed in 1986 by Czarnocki and co-workers,<sup>35</sup> during their synthesis of the enantiomers of the highly useful aldehyde **33a**, also employed as a calycotomine precursor in other synthetic protocols (Scheme 3). These authors prepared racemic calycotomine in unspecified yield by reaction of homoveratrylamine **29** and diethyl oxalate by the Grüssner procedure,<sup>36</sup> employing **30** and **31** as intermediates. The natural product was resolved with (–)-tartaric acid in a procedure which resembles that previously reported by Brossi, who used (+)-tartaric acid for an analogous purpose.<sup>37</sup> The resulting (+)- and (–)-calycotomine were independently treated with ethyl chloroformate (shown only for the *R* enantiomer) and, after basic hydrolysis to the corresponding ethyl carbamate **32**, submitted to a Swern oxidation, furnishing the required aldehyde **33a**.

In 1961, Benington and Morin<sup>38</sup> examined the Bischler–Napieralski cyclization of *N*-alkoxyacetyl homoveratrylamines **34a,b** (Scheme 4), available by treatment of homoveratrylamine **29** with methoxy- and benzyloxy-acetyl chloride.

Unexpectedly, neither phosphorus pentoxide nor phosphorus oxychloride, two of the most usually employed cyclization agents in the Bischler–Napieralski protocol, gave the required 3,4-dihydroisoquinoline **36**. However, the use of phosphorus pentachloride furnished 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**37**), after catalytic hydrogenation (10% Pd/C, methanol) of the cyclized product, which proved to be the chloride **35**. Unfortunately, the latter failed to be converted into calycotomine when treated with silver oxide or sodium acetate in methanol. Interestingly, however, allylic chloride **35** was employed as starting material for the preparation of some bioactive compounds.<sup>39</sup>

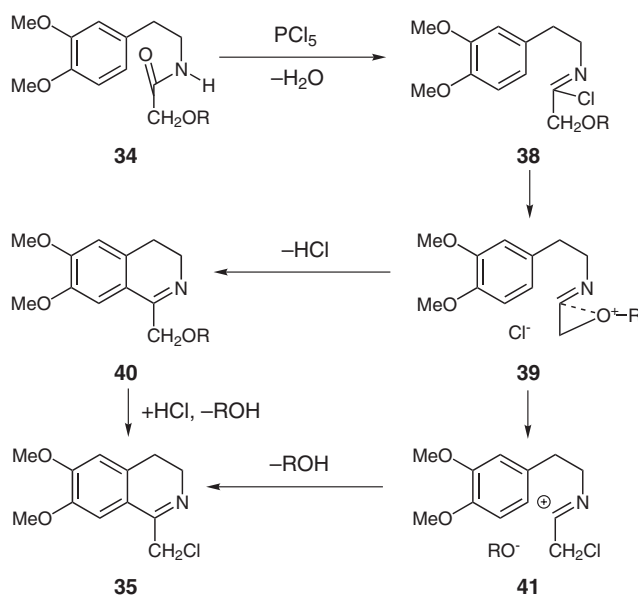
These observations were rationalized assuming that during the cyclization with phosphorus pentachloride, an imino chloride **38** is formed (Scheme 5). This, in turn, transforms into a cyclic oxonium ion **39** which, after displacement of the alkoxy group by chloride anion produces a carbonium ion **41** and internally cyclizes via an electrophilic attack of the aromatic nucleus.

In an alternative pathway, elimination of HCl from **39** generates the 1-alkoxymethyl derivative **40**, which can



Scheme 4

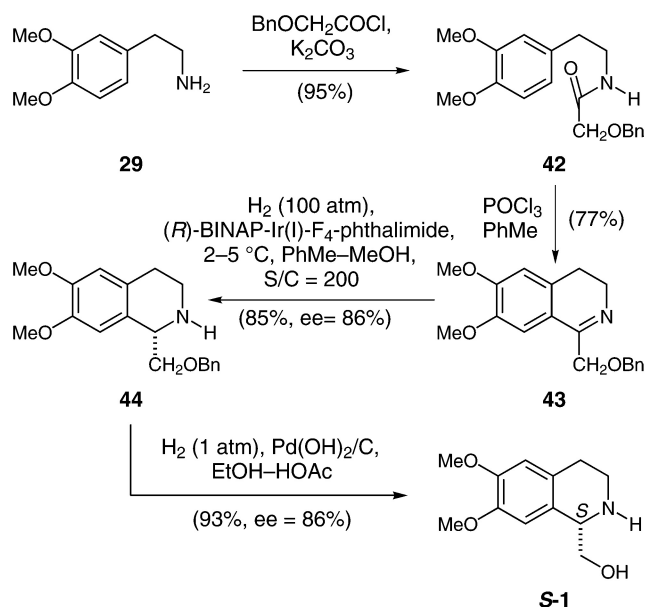
undergo nucleophilic displacement to furnish the chloride **35**. The fact that the 1-alkoxymethyl compound **40** was isolated from the reaction mixture seems to favor the latter mechanism, in which the cyclization takes place before ether cleavage.



Scheme 5

A modern version of the Benington and Morin sequence was recently disclosed by Morimoto and co-workers,<sup>40</sup> resulting in a highly enantioselective synthesis of (*S*)-calycotomine.<sup>41</sup> As shown in Scheme 6, this group prepared 1-benzyloxymethyl-3,4-dihydroisoquinoline (**43**) by the Bischler–Napieralski ring closure of amide **42** with phosphorus oxychloride and submitted the heterocyclic product to an asymmetric catalytic hydrogenation with (*R*)-BINAP-iridium(I) phthalimide catalysts.<sup>42</sup>





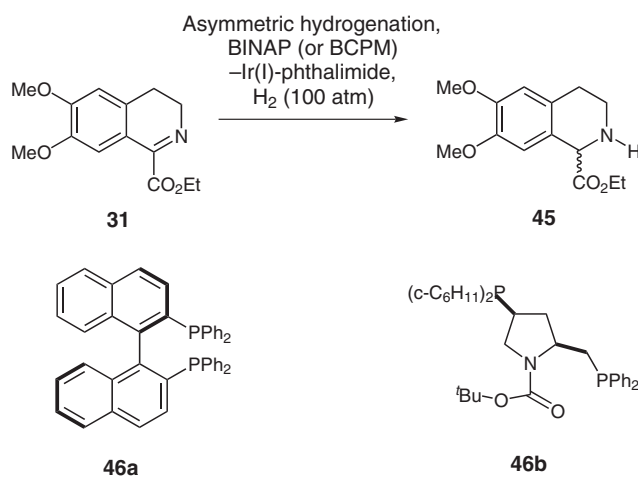
Scheme 6

Under these conditions, the imine double bond was selectively reduced, furnishing benzyloxy calycotomine **44** in 85% yield and 75% enantiomeric excess. The nature of the chiral ligand proved to have influence on the reaction outcome; when 3,4,5,6-tetrafluorophthalimide was employed instead of phthalimide, the asymmetric induction increased to an ee of 86%, which was improved to 96% after recrystallization of the product from toluene.

Catalytic hydrogenolysis of the benzyl ether moiety of **44** proved difficult with palladium on carbon. It also gave poor yields with palladium black and formic acid as hydrogen source, but proceeded readily with palladium hydroxide on carbon, giving access to the natural product in 93% yield.

Addition of acetic acid to the hydrogenation medium prevented loss of optical purity during the debenzoylation stage. Interestingly, however, when the same catalytic enantioselective reaction was attempted on the known dihydroisoquinoline ethyl ester **31**, employing either *R*-BINAP (**46a**) or 2*S*,4*S*-BCPM (**46b**) iridium(I) phthalimide complexes, the reaction proceeded very slowly, furnishing essentially the racemic tetrahydroisoquinoline ester **45** (Scheme 7). In addition, the asymmetric hydrosilylation of **31** with diphenylsilane and several chiral rhodium complex catalysts also gave unsatisfactory results.

Instead of employing tartaric acid and derivatives as resolving agents, other enantioselective syntheses of calycotomine and derivatives by the Bischler–Napieralski cyclization protocol, such as that depicted in Scheme 8, resorted to the use of these easily available chemicals as chiral inductors. In 1976, Dörnyei and Szántay<sup>43</sup> first described the Bischler–Napieralski-mediated synthesis of the enantiomer of **47** employing a tartrate ester.<sup>43,44</sup> Chemical manipulation of **47**, prepared with the aid of dimethyl tartrate **46c**, allowed Czarnocki and coworkers to synthesize aldehydes **33a,b**,<sup>45</sup> which are structurally related to



Scheme 7

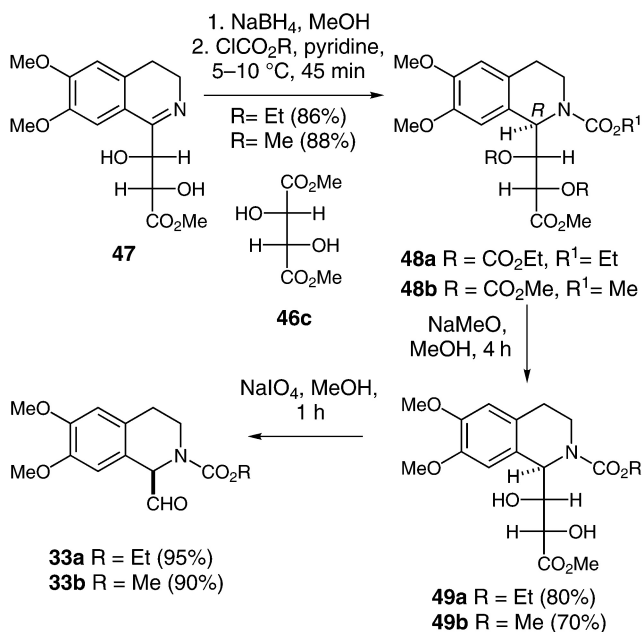
calycotomine and useful for its synthesis as well as for the elaboration of other, more complex, natural products.

Enantiomerically pure dihydroisoquinoline **47** was stereospecifically reduced to the corresponding (1*R*)-tetrahydroisoquinoline enantiomer. Treatment of the latter with excess methyl or ethyl chloroformate provided the dicarbonates **48a** and **48b**, respectively, which were partially deprotected by basic hydrolysis to carbamate diols **49a** and **49b**, the overall process implying the selective carbamoylation of the isoquinoline nitrogen moiety. Finally, sodium periodate cleavage of the diols gave aldehydes **33a** and **33b** in over 90% yield.

Aldehydes **33a** and **33b** were also obtained by the Pictet–Spengler methodology (see Section 3); however it was demonstrated that this Bischler–Napieralski approach has several advantages, since fewer steps are involved for the preparation of the immediate precursor to the aldehyde and the reaction leading to the generation of the asymmetric C-1 center is stereospecific. Moreover, optically active calycotomine can be obtained by this sequence in more than 30% overall yield from tetrahydroisoquinolines **49**, while the Pictet–Spengler route delivers the natural product in only 22% yield.

In this early approach to the enantioselective synthesis of calycotomine precursors by the Bischler–Napieralski route, the efficient chiral-inducing capabilities of tartaric acid were seemingly successfully used; however, part of its carbon skeleton was discarded. In a more recent and elaborated approach (Scheme 9), Czarnocki disclosed the utilization of all four of the carbon atoms of tartaric acid, which means employing both chiral centers of the diacid, in a synthesis of *N*-acetylcalycotomine.<sup>46</sup>

To this end, homovertrylamine **29** was condensed with dimethyl tartrate **46c**, furnishing diamide **50** in nearly quantitative yield. Acetylation of the diamide provided the diacetate **51**, which, once submitted to the Bischler–Napieralski cyclization with phosphorus pentachloride in methylene chloride, gave an unstable product, presumably a mixture of dihydroisoquinolines **52** and **53**. Sodium



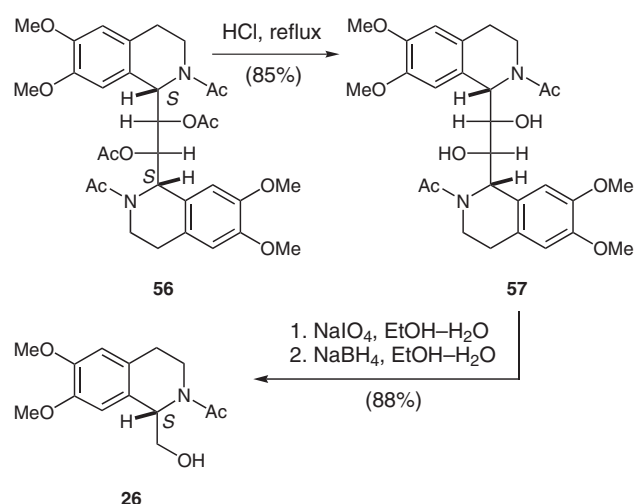
Scheme 8

borohydride reduction of the dihydroisoquinolines and acetylation of the product furnished a separable mixture of tetrahydroisoquinoline derivatives **54** and **55** in combined 84% yield. The same three-step sequence applied to **55** served to access bis(tetrahydroisoquinoline) **56** in 61% yield.

Finally, hydrochloric acid-mediated hydrolysis of the acetate groups of **56** gave 85% of diol **57** (Scheme 10) which, once submitted to sodium periodate cleavage followed by sodium borohydride reduction of the resulting aldehyde, provided *N*-acetylcalycotomine **26**<sup>47a</sup> in 88% yield. Determination of the enantiomeric composition of

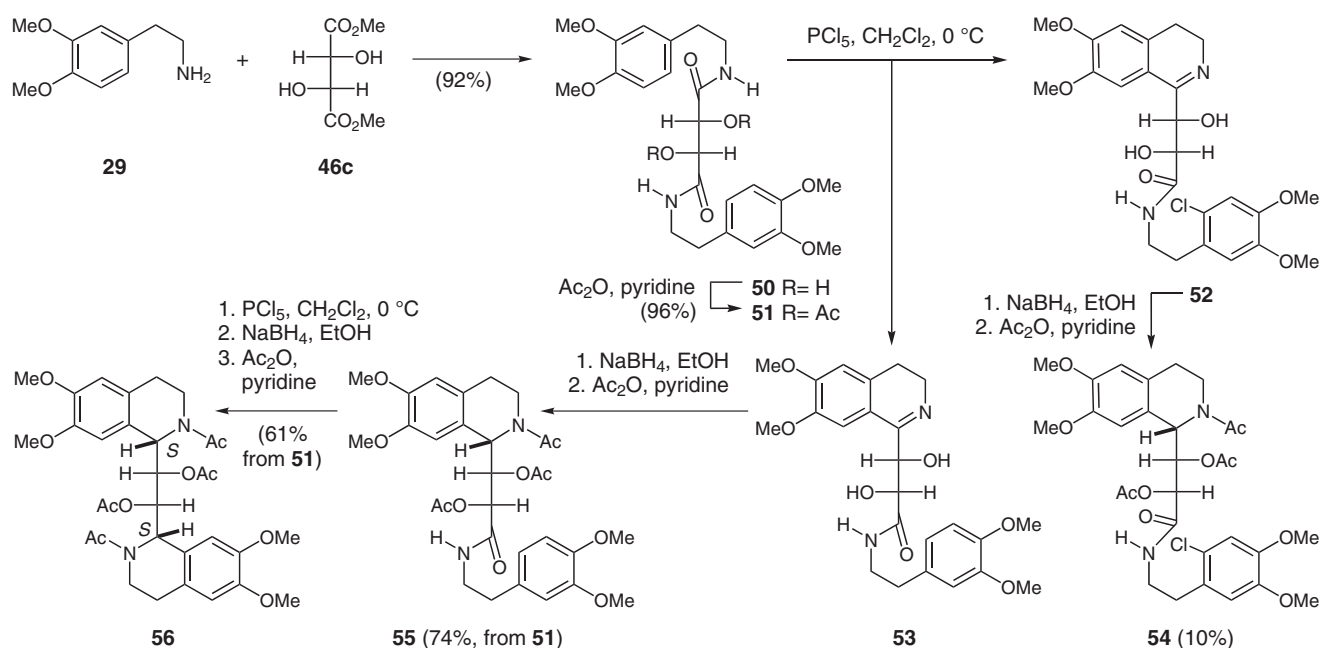
the thus obtained *N*-acetylcalycotomine was carried out by <sup>19</sup>F NMR analysis of the Mosher ester derivative formed with (+)-MTPA. The enantiomeric excess of the product proved to be more than 98% and the X-ray diffraction data of the acetate of (*S*)-**26** have been disclosed.<sup>47b</sup>

A somewhat similar sequence involving a L-(+)-tartaric acid ester and a Bischler–Napieralski-type cyclization has been recently disclosed for the synthesis of 1-hydroxy-methyl-β-carboline, enantioselectively leading to the 1*R* derivative.<sup>47c</sup>

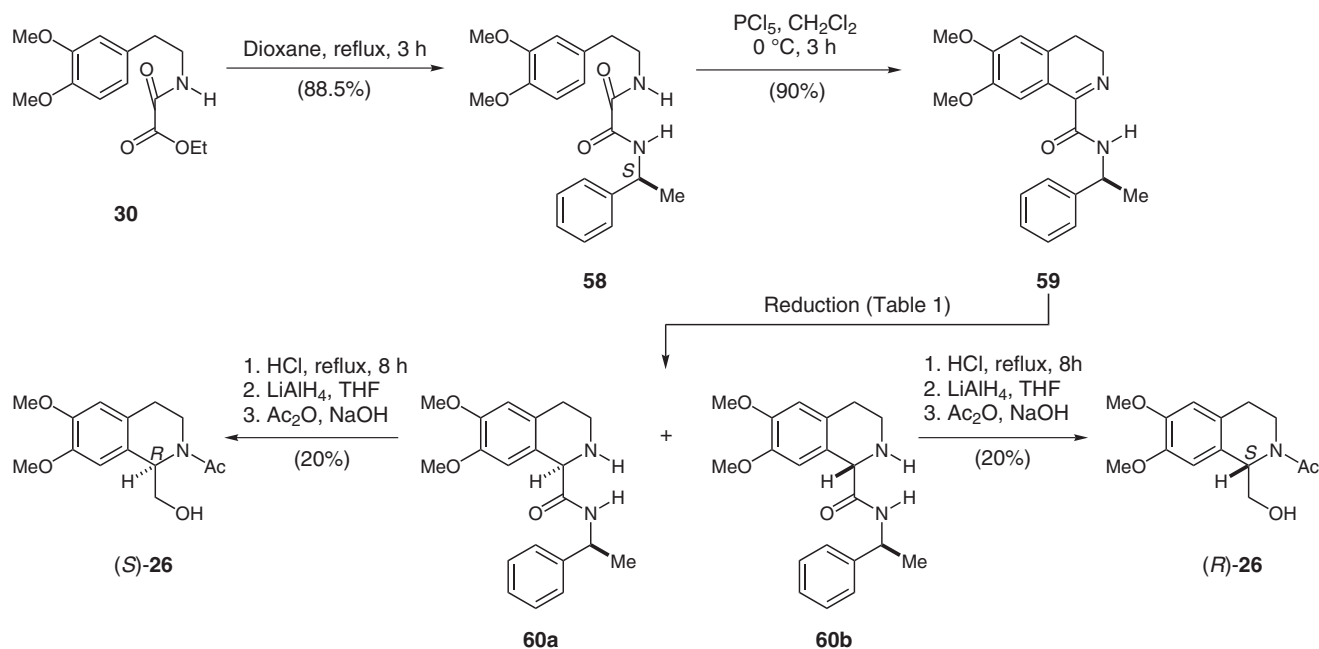


Scheme 10

In yet another approach to *N*-acetylcalycotomine **26** in chiral form, Czarnocki and coworkers<sup>48</sup> employed the versatile (*S*)-α-phenethylamine as chiral inductor (Scheme 11).<sup>49</sup> Their synthesis began with the known



Scheme 9



Scheme 11

amide ester **30**,<sup>31c</sup> easily available from homoveratrylamine **29**. This was submitted to an amidation with the chiral auxiliary and the resulting bis-amide product **58** was subjected to a Bischler–Napieralski cyclization with phosphorus pentachloride, furnishing chiral dihydroisoquinoline **59**. Upon reduction of the imine moiety, diastereomeric amines **60a** and **60b** were obtained, the proportion of which was observed to be influenced by the nature of the reducing agent and the reduction conditions, as shown in Table 1. X-ray studies carried on amine **60b** allowed the unequivocal establishment of the absolute configuration of the newly formed chiral center. The chromatographically separated tetrahydroisoquinolines displayed enantiomeric excesses higher than 98%, according to  $^{19}\text{F}$  NMR experiments carried out on the Mosher ester derivatives of the final products.

D-Ribonolactone **61** is a commercially available sugar which has found some use as a chiral source for the enan-

tioselective synthesis of non-sugar natural products.<sup>50a</sup> With the aid of D-ribonolactone as chiral inductor, Czarnocki and co-workers reported a synthesis of calycotomine which is formally analogous to that disclosed employing tartaric acid derivatives, and furnishes the 1*R* enantiomer of the natural product (Scheme 12).<sup>50b</sup>

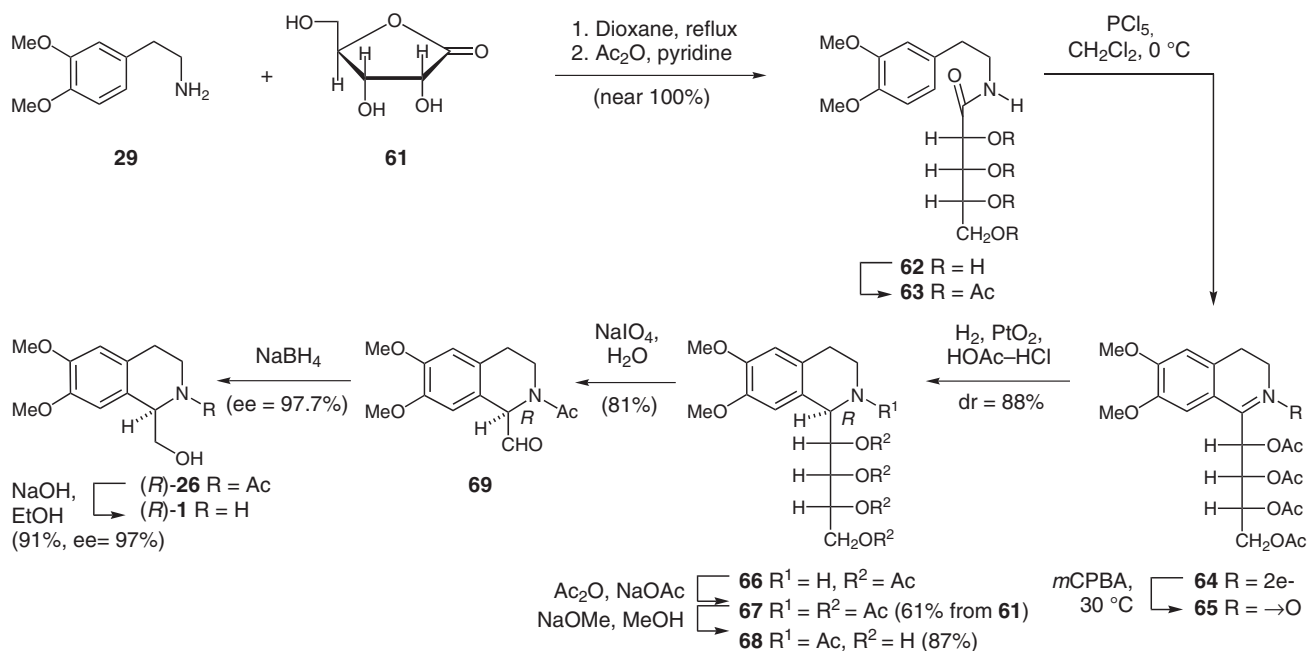
The lactone was condensed with homoveratrylamine (**29**), furnishing the expected amide **62**, which was peracetylated under conventional conditions to tetraacetate **63**. Mild Bischler–Napieralski cyclization with phosphorus pentachloride gave the corresponding 3,4-dihydroisoquinoline **64**, which unexpectedly proved to be highly unstable and could not be reduced to the required tetrahydroisoquinoline either with hydrides or by catalytic hydrogenation. Fortunately, however, oxidation of **64** with *m*-CPBA gave the stable nitron **65**<sup>50c</sup> which was readily reduced to a 94:6 mixture of diastereomeric tetrahydroisoquinolines **66**, with the C-1-(*R*) diastereomer prevailing.

Acylation of the most abundant tetrahydroisoquinoline, which gave **67** in 61% yield from D-ribonolactone, was followed by hydrolysis of the resulting tetraacetate to **68** and oxidative glycol cleavage of the tetraol **68** to aldehyde **69**, obtained in 81% yield. Finally, sodium borohydride reduction provided *N*-acetylcalycotomine (**26**), the deacetylation of which gave 91% of the *R*-enantiomer of the natural product (*R*)-**1** in excellent optical purity. Interestingly, the *N*-acetyl aldehyde **69** was an unisolated intermediate in Brossi's conversion of dehydromethopholine into *N*-acetylcalycotomine **26**,<sup>37</sup> and its *S*-enantiomer was prepared by Czarnocki from **29** and vitamin C (L-ascorbic acid, another inexpensive chiral source)<sup>47a,50d–f</sup> through the intermediacy of L-(+)-gulono-1,4-lactone,<sup>50g,h</sup> following a Bischler–Napieralski type strategy very similar to that depicted in Scheme 12.

**Table 1** Diastereoselective Reduction of 3,4-Dihydroisoquinoline **59**

Entry	Substrate	Conditions	Diastereomeric ratio
1	<b>59</b> ·HCl	$\text{NaCNBH}_3$ , AcOH, $\text{CH}_2\text{Cl}_2$ , $0^\circ\text{C}$	49:51
2	<b>59</b>	$\text{H}_2$ , $\text{PtO}_2$ , $0^\circ\text{C}$	44:56
3	<b>59</b> ·HCl	$\text{H}_2$ , $\text{PtO}_2$ , $0^\circ\text{C}$	42:58
4	<b>59</b>	$\text{NaBH}_4$ , EtOH, r.t.	66:34
5	<b>59</b>	$\text{NaBH}_4$ , EtOH, $-78^\circ\text{C}$	88:12
6	<b>59</b> ·HCl	$\text{NaBH}_4$ , EtOH, HCl, $-20^\circ\text{C}$	40:60
7	<b>59</b>	$\text{H}_2$ , $\text{RhCl}(\text{PPh}_3)_3$ , 100 atm, r.t.	9:81



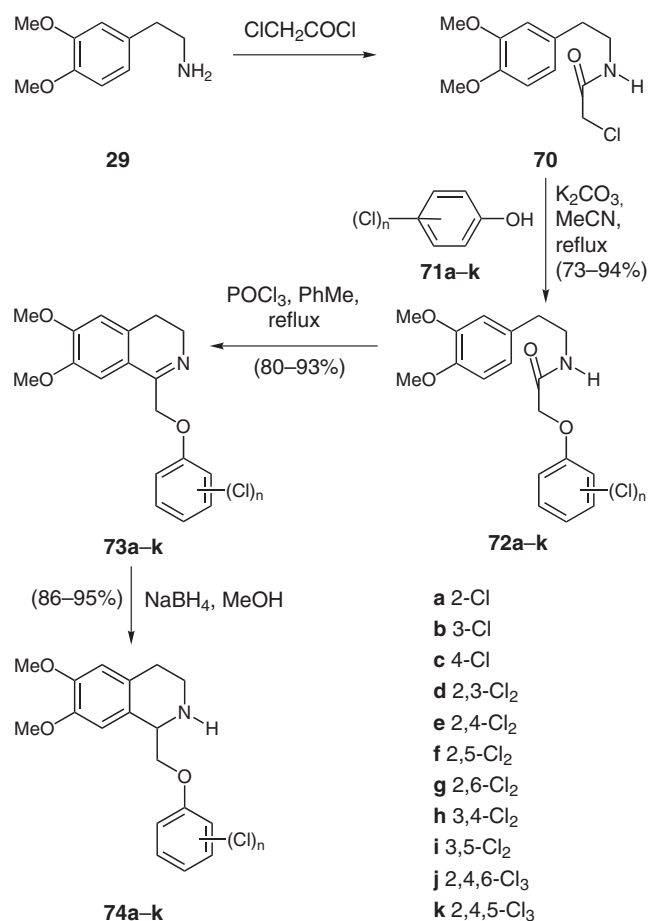


Scheme 12

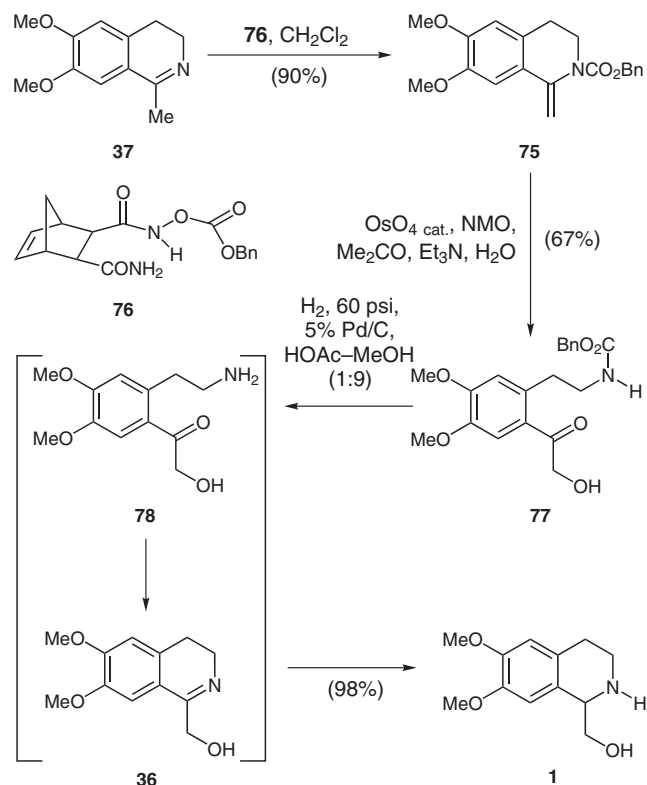
For the pharmacological characterization of the action of tetrahydroisoquinoline derivatives on isolated rat and guinea pig tracheae, Yoon<sup>51a</sup> prepared phenoxy derivatives of calycotomine by the conventional Bischler-Napieralski approach. In their synthesis (Scheme 13), 3,4-dimethoxyphenethylamine (**29**) was conveniently acylated with monochloroacetyl chloride, furnishing amide **70**,<sup>51b,c</sup> which was reacted with a series of polychlorosubstituted phenols **71a–k** under base promotion to give the corresponding phenolic ethers **72a–k** in 81–94% yield. In turn, these were cyclized with phosphorus oxychloride in refluxing toluene to give 80–93% of 1-aryloxymethylene-3,4-dihydroisoquinolines **73a–k** and finally reduced with sodium borohydride to the corresponding polychlorinated tetrahydroisoquinolines **74a–k** in 86–95% yield.

In an alternative strategy, Lenz<sup>52</sup> took advantage of the easy formation of 3,4-dihydroisoquinolines as Bischler-Napieralski reaction products<sup>53a</sup> and their facile transformation into enamides<sup>53b</sup> to develop an ingenious type 2 synthesis of calycotomine by conversion of an enamide into the related aminoalcohol (see section 1).

In this protocol (Scheme 14), the known dihydroisoquinoline **37**<sup>53a,54</sup> was converted into enamidocarbonate **75**, with carbamate **76** as a convenient benzyloxycarbonyl transfer reagent.<sup>55</sup> Next, compound **75** was easily oxidized to the open hydroxyketone **77** with catalytic osmium tetroxide and NMO as stoichiometric oxidant. Hydrogenolytic deprotection of the benzyl carbamate moiety provided an amine intermediate **78**, which spontaneously cyclized, with concomitant dehydration, to give 1-hydroxymethyl-3,4-dihydroisoquinoline (**36**). This was finally transformed into racemic calycotomine in 98% overall yield from **77** by means of a catalytic hydrogenation of its double bond.



Scheme 13

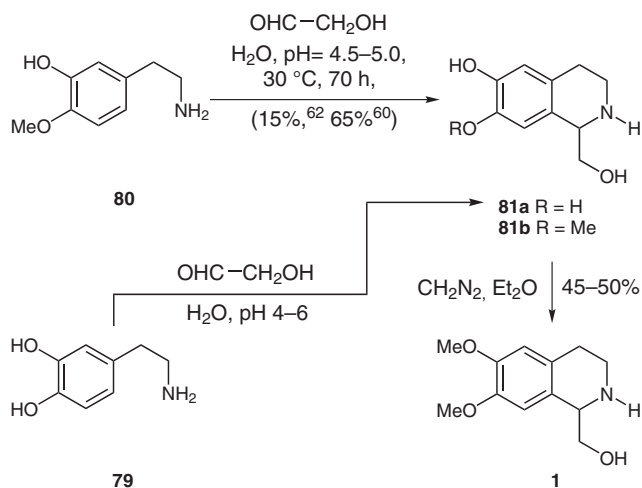


Scheme 14

### 3 Pictet–Spengler Condensation

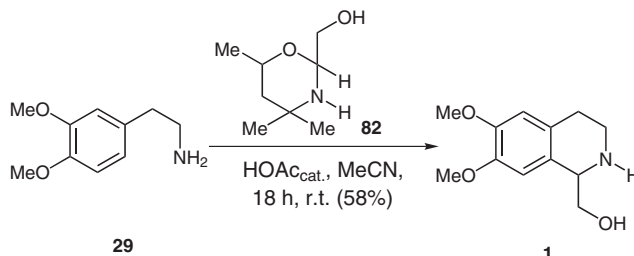
This was the first synthetic strategy used towards calycotomine; however, the literature records that success of the condensation reaction of glycolaldehyde with the different  $\beta$ -phenethylamine derivatives employed is strongly dependent on the reaction conditions and the degree of activation of the aromatic ring. An early attempt by White for preparing the natural product by condensation of homoveratrylamine (**29**) with glycolic aldehyde met with failure.<sup>56</sup> However, this scientist was able to achieve the synthesis of 6,7-demethylcalycotomine (**81a**)<sup>20b</sup> by the Pictet–Spengler condensation of this simple aldehyde with 3,4-dihydroxy- $\beta$ -phenethylamine (dopamine, **79**, Scheme 15).<sup>57</sup> In addition, it was also shown that condensation of glycolic aldehyde with 3-hydroxy-4-methoxyphenethylamine (homoisovanillylamine, **80**),<sup>58</sup> according to the method of Beke<sup>59</sup> at pH 5, in spite of the latter being more activated than **29**, furnished only poor yields of 1-hydroxymethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**81b**) after 70 hours at 30 °C. This finally gave calycotomine upon O-methylation with ethereal diazomethane. With only subtle changes in reaction conditions, the same strategy furnishing calycotomine in 30% overall yield, was disclosed by Chatterjee and Adityachaudhury in 1962.<sup>60,61</sup>

Sha and co-workers effected similar experiments; however, in their hands the reaction of glycolic aldehyde with dopamine (**79**) met with failure,<sup>62</sup> while the analogous



Scheme 15

transformation, with  $\beta$ -phenethylamine derivative **80** was successful, but yielded 6-demethyl calycotomine (**81b**) in poor yield (15%), in spite that variations in time and pH were tried. The product was transformed into calycotomine by O-methylation with diazomethane (Scheme 15). Singh and Singh<sup>63a</sup> studied the use of perhydroxazines as activated carbonyl equivalents in the Pictet–Spengler condensation (Scheme 16). The reaction of homoveratrylamine (**29**) and 2-hydroxymethyl-4,4,6-trimethyltetrahydro-(2*H*)-1,3-oxazine (**82**) as a two-carbon unit in anhydrous acetonitrile containing a catalytic amount of acetic acid provided 58% of calycotomine, after 18 hours at room temperature.



Scheme 16

The key oxazine is readily available from hydroxyacetonitrile<sup>63b</sup> and in practice, this synthesis involves the use of a masked form of glycolic aldehyde to perform a Pictet–Spengler cyclization that cannot be carried out with glycolic aldehyde itself.

Interestingly, however, an intramolecular Pictet–Spengler cyclization with glycolic aldehyde, masked as an acetal ester, served Corey and Gin as the key step for the enantioselective synthesis of a 1-hydroxymethyl-substituted tetrahydroisoquinoline embodying the AB ring system of ecteinasidine **743**.<sup>64</sup>

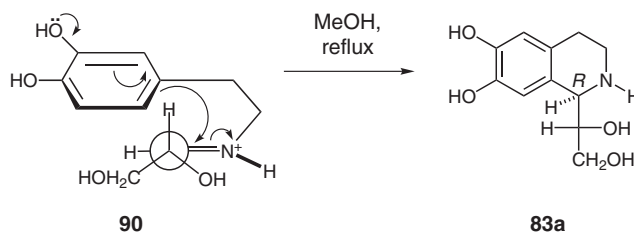
Carbohydrates and other polyhydroxylated compounds have been used for the stereoselective synthesis of alkaloids due to their ready availability in pure enantiomeric

form.<sup>65</sup> Czarnocki and co-workers found that sugars can be used as starting materials in the Pictet–Spengler condensation.<sup>66</sup> Accordingly, they developed Pictet–Spengler-type syntheses of calycotomine and derivatives in their optically active forms employing polyhydroxylated aldehydes as carbonyl components for the cyclization with dopamine hydrochloride **79·HCl**.<sup>67</sup>

In their synthesis (Scheme 17), amine **79** was condensed with (+)-glyceraldehyde and the resulting diastereomeric tetrahydroisoquinolines **83** were subjected to reaction with excess ethyl chloroformate, furnishing a separable mixture of tetracarboxates **84**. The major diastereomer with the *1R* configuration, **84a**, was partially hydrolyzed with base to give **85** and methylated under Williamson conditions, yielding 6,7-dimethoxy tetrahydroisoquinoline **86**. Sodium periodate cleavage of the diol gave an unstable aldehyde **33a**, which upon reduction furnished alcohol **87**. Finally, reduction of **87** gave *N*-methylcalycotomine **88**,<sup>68</sup> while basic hydrolysis provided *R*-calycotomine in 90% enantiomeric excess, through the intermediacy of the previously known oxazolo[4,3-*a*]isoquinoline **89**.<sup>69</sup>

Selectivity of the cyclization to provide preferentially the *1R* diastereomer **83a** was explained as shown in Scheme 18, employing an analogy to Cram's rule<sup>70</sup> where attack to the intermediate iminium ion **90** formed by condensation of dopamine with chiral glyceraldehyde takes place from the least hindered side.

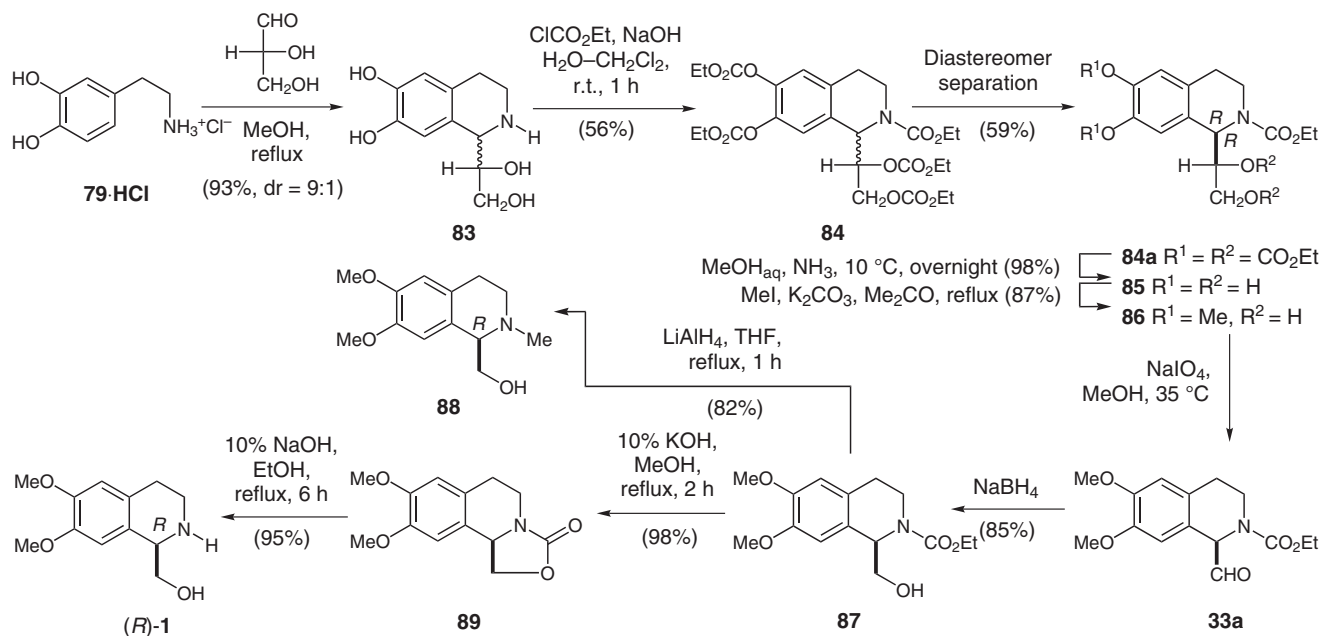
The synthesis of *S*-**83b**, the enantiomer of the calycotomine precursor prepared by Czarnocki in Scheme 17, through an alternative synthetic route involving an aryl radical cyclization, was reported in 1993 by Tomaszewski and Warkentin.<sup>71a</sup>



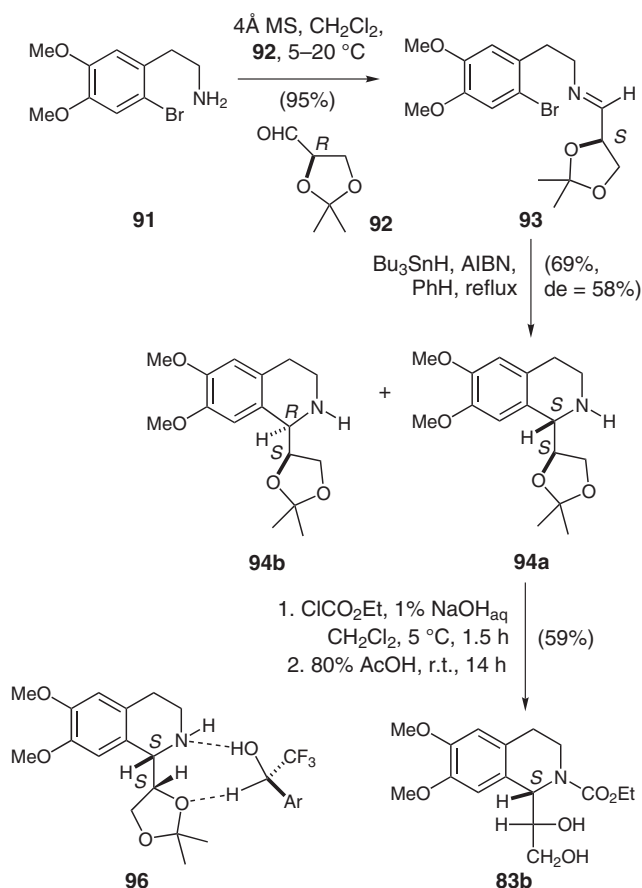
Scheme 18

As shown in Scheme 19, reaction of 6-bromohomoveratrylamine (**91**) with the *R*-acetonide of glyceraldehyde (**92**) furnished an imine intermediate **93**, which upon submission to the tributyltin hydride–AIBN mixture in refluxing toluene afforded 69% of the diastereomeric mixture of **94a** and **94b** in 58% diastereomeric excess, favoring the (*S,S*) compound. Exposure of **94a** to ethyl chloroformate, followed by hydrolysis of the acetonide moiety, furnished **83b**. The configuration of the newly formed stereocenter was inferred from results of NMR experiments with chiral agents, such as that shown in **96**. This cyclization proceeded exclusively in a 6-*endo* fashion and no products derived from the 5-*exo* alternative pathway were observed.<sup>71b</sup>

A synthesis of *N*-methylcalycotomine (**88**) proceeding along similar lines (Scheme 20) was more recently reported by the group of Czarnocki.<sup>72</sup> This novel protocol employs (*2R*)-*N*-glyoxylbornane-10,2-sultam (**97**), a stable hemiacetal widely employed in as a chiral aldehyde moiety Diels–Alder chemistry.<sup>73</sup> Condensation of **97** with dopamine (**79**) gave a separable 89:11 mixture of diastereomeric unstable tetrahydroisoquinoline derivatives **98**. Upon isolation of the major diastereomer **98a** in 57% yield, this was protected as the methyl carbamate **99** and submitted to mild ammonolysis and di-*O*-methylation,



Scheme 17



Scheme 19

furnishing the amidoester **100** in 87% yield. Final treatment of both reducible functional groups of **100** with lithium aluminum hydride gave 91% yield of *N*-methylcalycotomine (**88**),<sup>68</sup> of known absolute configura-

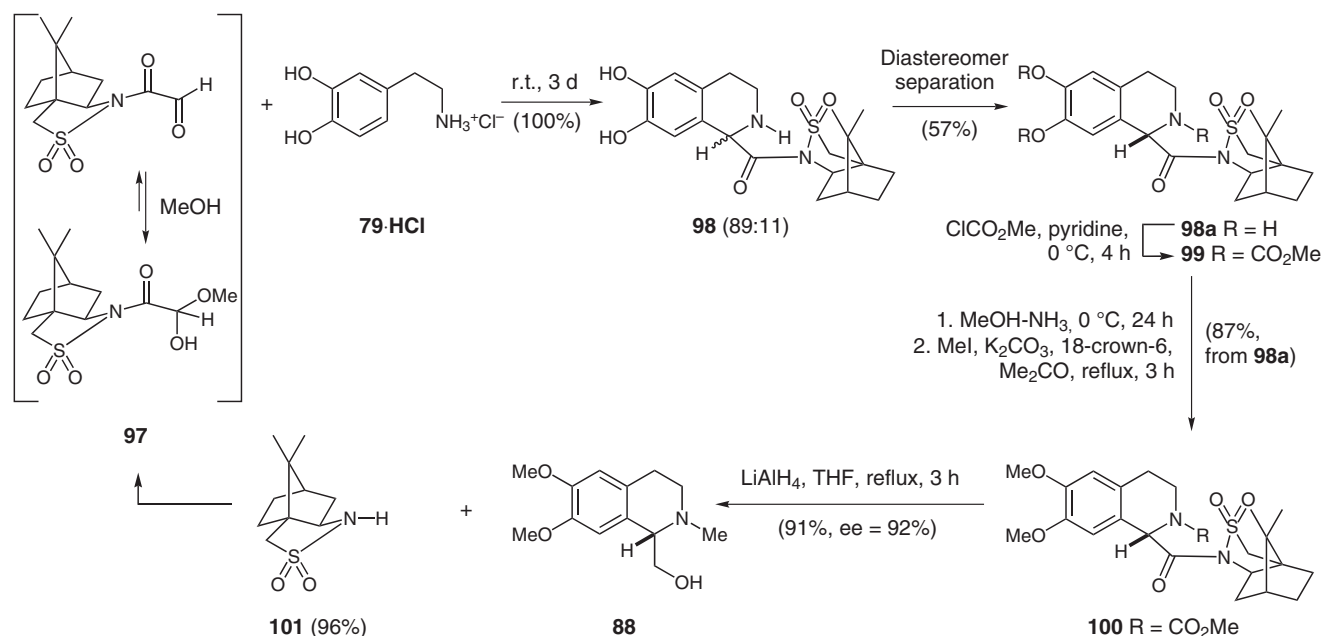
tion. Chiral <sup>1</sup>H NMR employing Eu(hfc)<sub>3</sub> as chiral shift reagent revealed that the enantiomeric excess of the product was 92%. Interestingly, chiral auxiliary **101** was recovered in 96% yield, without loss of optical purity.

Employing a related approach, Silveira and co-workers reported a total synthesis of calycotomine resorting to the use of  $\alpha$ -chloro- $\alpha$ -phenylselenoesters as masked aldehydes (Scheme 21).<sup>74</sup> In their activated Pictet–Spengler scheme, *N*-tosyl- and *N*-camphorsulfonyl-homoveratrylamines (**102a** and **102b**) were condensed with ethyl  $\alpha$ -chloro- $\alpha$ -phenylselenoacetate, as glyoxylic acid surrogate, under the assistance of tin(IV) chloride, furnishing **103a** and **103b** in 72% and 60% yield, respectively.

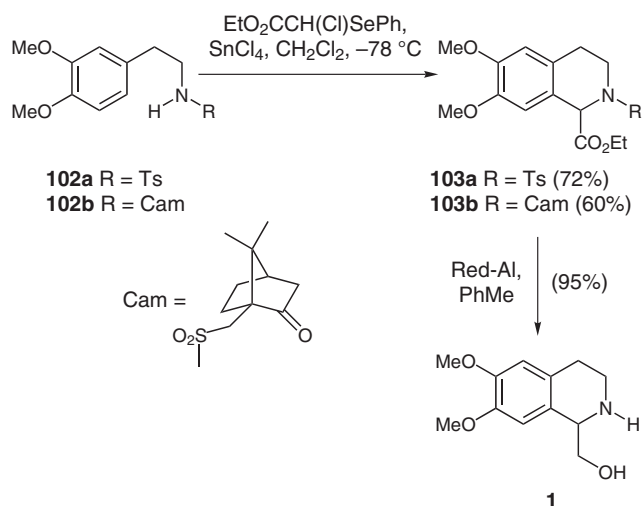
Interestingly, in the latter case, a 1:1 mixture of diastereomers was isolated. To complete the synthesis, **103a** was submitted to a reductive desotylation with Red-Al in refluxing toluene, which occurred with concomitant reduction of the ester moiety, providing calycotomine in 95% yield.

A related synthesis of structurally similar compounds by the activated Pictet–Spengler protocol was reported more recently by a Korean team. In their approach, methanesulfonyl derivatives of homoveratrylamine, **104a–d**, were condensed with bromoacetal or L-menthyl glyoxylate **105**, furnishing 6,7-dimethoxy tetrahydroisoquinolines **106** and/or their 7,8-dimethoxy-substituted congeners **107**, as shown in Table 2.

The synthesis of an enantiopure 1-trifluoromethylated analog of *N*-methylcalycotomine, **113a**, was also reported. This new  $\beta$ -fluoroalkyl- $\beta$ -aminoalcohol is a member of a class of compounds important for their biological properties;<sup>75a</sup> the most known example of this compound class is Florfenicol, an antibiotic widely used in the animal health market. The synthesis of **113a**, which was prepared in



Scheme 20



Scheme 21

good overall yield<sup>75b</sup> starting from the  $\beta$ -imino sulfoxide **110**, is outlined in Scheme 22. Sulfoxide **110** is readily available by condensation of homoveratrylamine **29** with the trifluoroacetic acid–triphenylphosphine reagent in carbon tetrachloride, which yields vinyl chloride **108**, followed by substitution of the vinylic halogen group with the chiral lithium sulfoxide derivative **109**.

During the synthesis, imino sulfoxide **110** underwent stereoselective Pictet–Spengler-type cyclization under catalysis by trifluoroacetic acid, providing the cyclic *1S,SR* derivative **111** in 75% de. N-Methylation of the major dia-

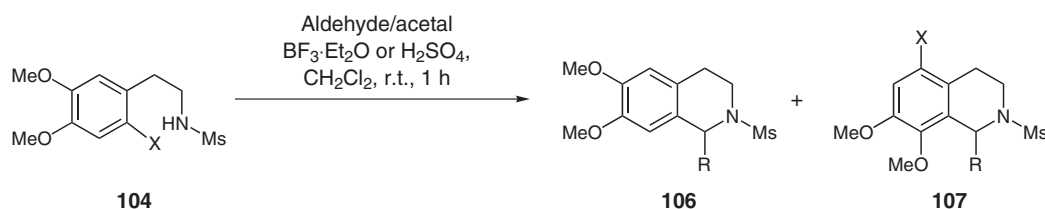
stereomer to **112** and normal Pummerer reaction,<sup>75c,d</sup> followed by hydrolysis of the resulting thioacetal intermediate with  $\text{K}_2\text{CO}_3/\text{HgCl}_2$ , afforded a highly stable quaternary  $\alpha$ -amino aldehyde, whose reduction with sodium borohydride delivered the target alkaloid **113a** in good overall yield.

The good diastereoselectivity of this intramolecular Pictet–Spengler reaction was explained by suggesting that, due to the *cis* geometry of the C=N bond of the substrate **110**, the electron-rich 3,4-dimethoxyphenyl group and the stereogenic *p*-tolylsulfinyl group were spatially close to each other during the cyclization.

Thus, the chiral sulfinyl auxiliary can exert a strong stereodirecting effect on the ring closure through a reactive conformation which minimizes the dipole–dipole interactions between the S=O and C=N bonds.<sup>75e–g</sup> Then, nucleophilic attack of the 3,4-dimethoxyphenyl group is induced to occur from the less hindered *re*-face of the stabilized carbocation on C-1 formed via protonation of the imine nitrogen of **110** by TFA.

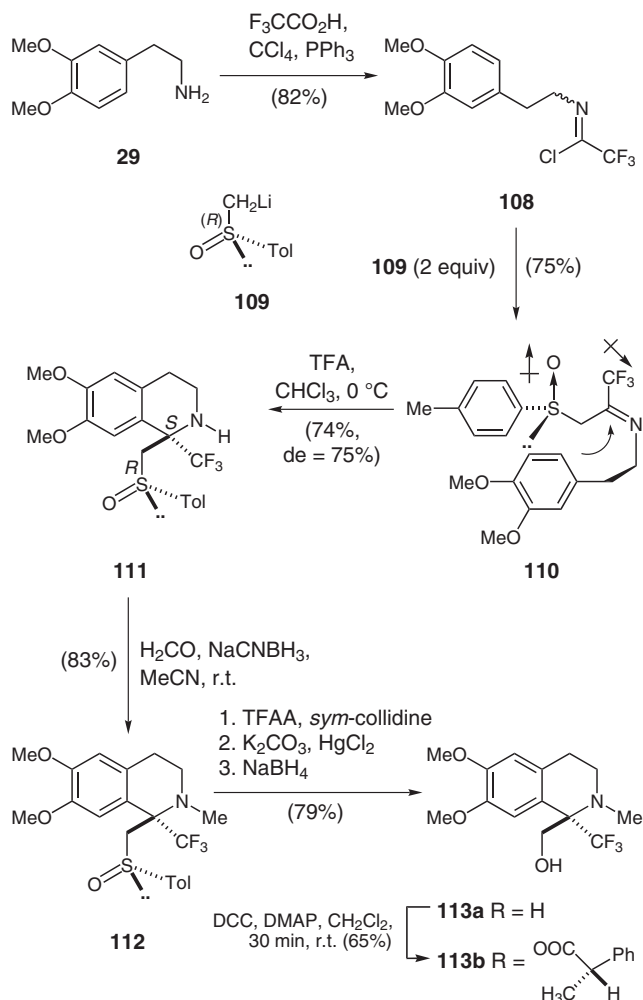
Esterification of (*R*)-**113a** with both enantiomers of  $\alpha$ -phenylpropionic acid and analysis of the resulting crude reaction mixtures of **113b** (and its diastereomer) by  $^1\text{H}$  and  $^{19}\text{F}$  NMR showed that the enantiomeric purity of the product was 75%. Finally, the stereochemistry of the quaternary trifluoromethyl-substituted stereogenic center C-1 was unequivocally determined by X-ray diffraction of a single crystal of **113b**, obtained by esterification of **113a** with (*1S*)- $\alpha$ -phenylpropionic acid in 65% yield.

**Table 2** Synthesis of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines Structurally Related to Calycotomine by the Activated Pictet–Spengler Approach



Entry	X	Compound	Aldehyde/acetal	R	Yield (%)	Ratio ( <b>106</b> : <b>107</b> )
1	H	<b>104a</b>		$\text{CH}_2\text{Br}$	95	100:0
2	Cl	<b>104b</b>	"	$\text{CH}_2\text{Br}$	90	0.2:99.8
3	Br	<b>104c</b>	"	$\text{CH}_2\text{Br}$	92	5.0:95.0
4	I	<b>104d</b>	"	$\text{CH}_2\text{Br}$	89	41.1:58.9
5	H	<b>104a</b>		$\text{CO}_2\text{-L-Menthyl}$	89	100:0
6	Cl	<b>104b</b>	"	$\text{CO}_2\text{-L-Menthyl}$	81	0:100
7	Br	<b>104c</b>	"	$\text{CO}_2\text{-L-Menthyl}$	76	12.8:87.2
8	I	<b>104d</b>	"	$\text{CO}_2\text{-L-Menthyl}$	83	61.4:38.6





Scheme 22

#### 4 Asymmetric Intramolecular Allylic Amination

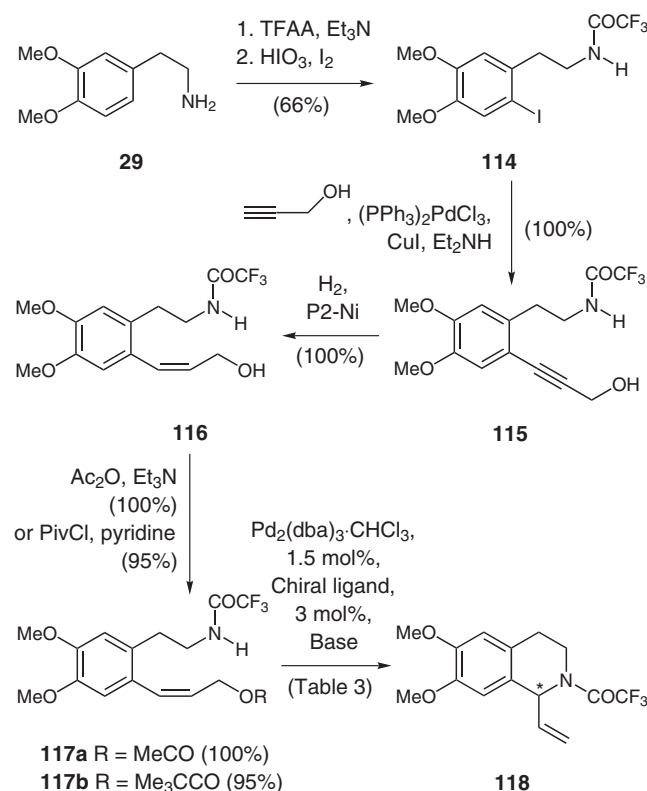
The catalytic enantioselective synthesis of natural products is one of the most recent and effective approaches to the acquisition of target compounds in chiral form and one of the most important innovations in organic synthesis. Almost all of the enantioselective syntheses of calycotomine described above relied on diastereoselective reactions for the introduction of chirality at C-1 and this required the use of stoichiometric amounts of the chiral source.

Furthermore, the asymmetric reduction of chiral 3,4-dihydroisoquinolines arising from the Bischler–Napieralski cyclization with optically active compounds employing hydrides gave sometimes poor selectivity and sporadically, unstable compounds were found in the synthetic routes. In addition, catalytic enantioselective hydrogenation was demonstrated to be just a moderately efficient approach for the elaboration of calycotomine, since only satisfactory optical yields of the natural product were realized; furthermore, the transformation required high pressures and specially designed catalysts.

The use of transition metal complexes as catalysts for organic transformations is currently a subject of intense activity and many endeavors. Among the reasons which explain this interest are the possibility, offered by organometallic complexes, to carry out transformations which are difficult or impossible through the methods of 'classical' organic chemistry, and the ability to control the selectivity associated with the transformation, i.e. the distribution of products, through the use of appropriate ligands.

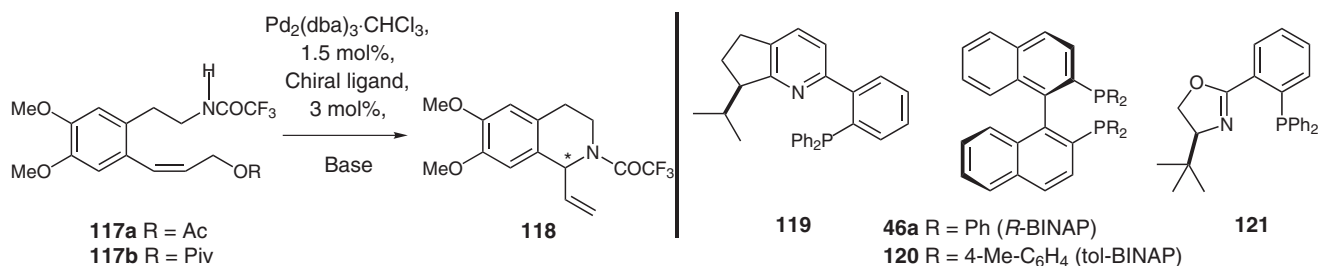
Very recently, a Japanese team headed by Katsuki<sup>76a</sup> disclosed a new palladium-catalyzed version of the asymmetric intramolecular allylic amination,<sup>76b</sup> potentially very useful for the elaboration of various 1-substituted tetrahydroisoquinolines. Their strategy, the power of which was tested in a new total synthesis of the naturally occurring carnegine (1,2-dimethyl-6,7-dimethoxy tetrahydroisoquinoline), used *N*-carboxyethyl calycotomine **87** as one of its advanced intermediates.

To that end, the known phenethylamine **29** was protected as its trifluoroacetamide derivative under conventional conditions and then nuclearily iodinated with the iodic acid–iodine reagent, furnishing **114** in 66% overall yield.



Scheme 23

Next, quantitative propargylation of **114** under palladium catalysis provided acetylene derivative **115**, which was partially reduced in quantitative yield to *Z*-olefin **116** with the assistance of a nickel catalyst. Acetylation and piv-  
aloylation of **116** afforded good yields of the correspond-

**Table 3** Optimization of the Catalytic Enantioselective Allylic Amination Reaction of **117a,b** Leading to 1-Vinyltetrahydroisoquinoline **118**

Entry	Olefin/Ligand	Base	Solvent	Temp. (°C)	Time	Yield:ee (Config.)
1	<b>117a/119</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	4 h	90:39 ( <i>R</i> )
2	<b>117a/119</b>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	r.t.	—	—
3	<b>117a/119</b>	—	DMF	60	18 d	52:67 ( <i>R</i> )
4	<b>117a/46a</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	4 d	83:53 ( <i>S</i> )
5	<b>117a/46a</b>	—	DMF	60	18 h	82:23 ( <i>R</i> )
6	<b>117a/120</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	4 d	76:24 ( <i>R</i> )
7	<b>117a/120</b>	Cs <sub>2</sub> CO <sub>3</sub>	DMF	60	24 d	51:32 ( <i>R</i> )
8	<b>117a/121</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	d	58:12 ( <i>R</i> )
9	<b>117a/121</b>	—	DMF	60	13 d	42:23 ( <i>R</i> )
10	<b>117b/46a</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	21 h	92:75 ( <i>R</i> )
11	<b>117b/119</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0	5 d	89:40 ( <i>R</i> )
12	<b>117b/119</b>	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	12 d	89:88 ( <i>R</i> )
13	<b>117b/119</b>	Na <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	23 d	49:88 ( <i>R</i> )
14	<b>117b/119</b>	Li <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	—	—
15	<b>117b/119</b>	—	DMF	60	23 d	58:82 ( <i>R</i> )
16	<b>117b/119</b>	—	DMF	60	3 h	76:79 ( <i>R</i> )
17	<b>117b/119</b>	—	DMF	100	3 h	78:77 ( <i>R</i> )
18	<b>117b/120</b>	Cs <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	36 d	63:33 ( <i>S</i> )

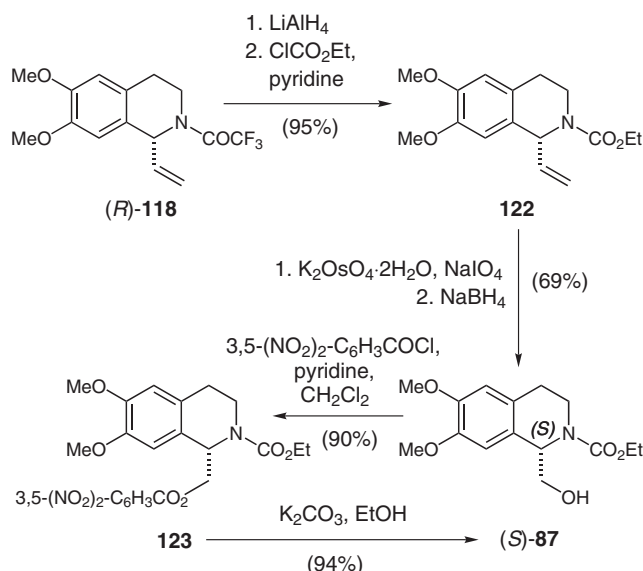
ing key intermediate esters **117a** and **117b**, as shown in Scheme 23.<sup>77a</sup>

As depicted in Table 3, optimization experiments carried out towards the elaboration of tetrahydroisoquinoline **118** were run in different solvents with both esters, employing alkaline carbonates or in the absence of base, with the aid of 3 mol% of chiral ligands **46a** and **119–121** and 1.5 mol% of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  as palladium source.

It was observed that the bulkier ester **117b** gave better enantiomeric excesses of product than its congener **117a**. The most convenient conditions (89% yield, 88% ee) were achieved when potassium carbonate was employed as base in the presence of pyridine derivative **119** as chiral ligand. On the other hand, BINAP derivatives **46a** and **120** performed as poor ligands and exhibited inversion of

the sense of asymmetric induction, depending on the reaction conditions (entries 4–7 and 18), while chiral oxazoline **121** offered unexpectedly poor chemical and optical yields of product.

Culmination of the synthesis was carried out as depicted in Scheme 24, by replacing the trifluoroacetamide group of (*R*)-**118** with an ethyl carbamate to give **122**. The extra carbon atom was removed by a Lemieux–Johnson oxidative fission of the vinyl group employing the potassium osmate–sodium periodate reagent system, followed by a reductive step to calycotomine derivative (*S*)-**87**. Transformation of (*S*)-**87** into the 3,5-dinitrobenzoate **123**, followed by fractional crystallization of the latter increased the ee of the product to 98%. Upon basic alcoholysis (EtOH, K<sub>2</sub>CO<sub>3</sub>), (*S*)-**87** was obtained in 94% yield.

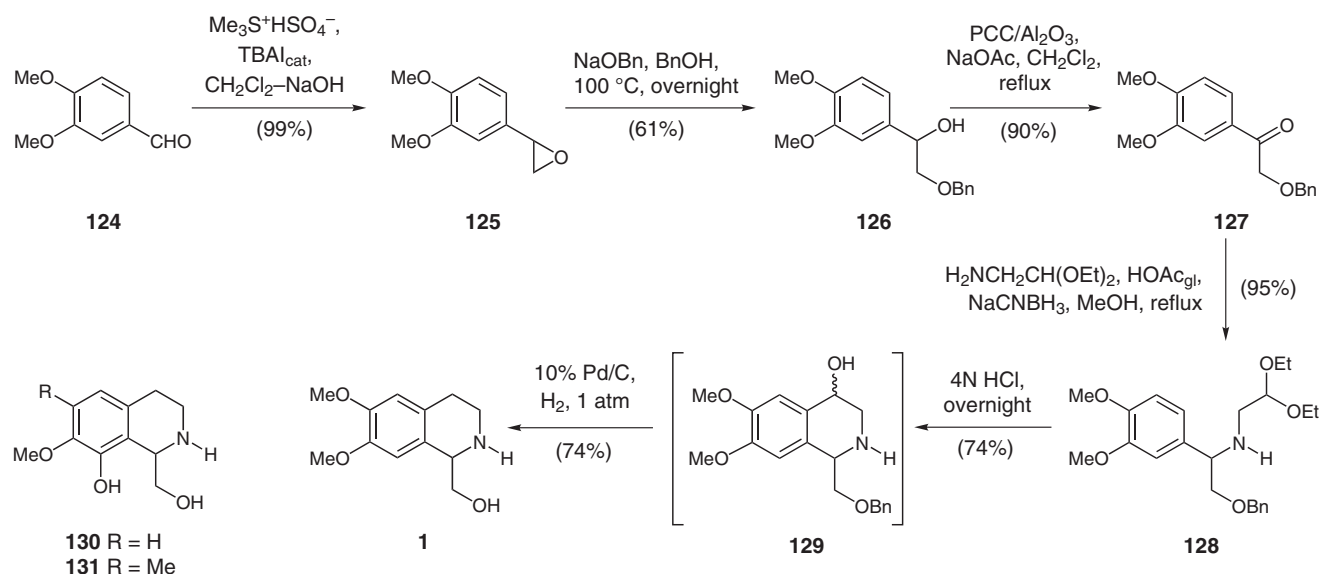


Scheme 24

## 5 Bobbitt Isoquinoline Synthesis

The Bobbitt acetal cyclization<sup>77</sup> is a modification of the classical Pomerantz–Fritsch isoquinoline synthesis, which is highly suitable for the preparation of tetrahydroisoquinolines; it belongs to type 5 of Kametani's classification of isoquinoline ring syntheses. Kaufman recently reported the only available example of a synthesis of calycotomine employing a type 5 synthetic approach through the use of Bobbitt's cyclization protocol.

Veratraldehyde (**124**) was submitted to a homologative epoxidation under the conditions of Merz and Märkl,<sup>78</sup> and the resulting epoxide **125**, obtained almost quantitatively, was nucleophilically opened with sodium benzyloxide in hot benzyl alcohol,<sup>79</sup> furnishing 61% of the required monoprotected glycol **126**.



Scheme 25

A PCC on alumina-mediated<sup>80</sup> oxidation of **126** to the related ketone **127**, followed by a reductive amination with aminoacetal, employing sodium cyanoborohydride as reducing agent, and dehydrating conditions to overcome the sluggishness of the reaction,<sup>81</sup> provided aminoacetal **128**. Cyclization with 4 N HCl<sup>82</sup> led to intermediate **129** which was then submitted to a Pd/C hydrogenolysis,<sup>83a</sup> giving the natural product in good overall yield (Scheme 25).

Essentially the same strategy was applied for the syntheses of 1-hydroxymethyl tetrahydroisoquinoline derivatives **130** and **131**,<sup>83b</sup> which are partial analogs of the  $\beta$ -adrenergic receptor inhibitor MY336-a (**6**). In the case of **131**, however, the Jackson modification of the Pomerantz–Fritsch isoquinoline synthesis was required in order to bring about cyclized products.

Other interesting modifications of the Pomerantz–Fritsch cyclization protocol were reported as useful for the preparation of 1-hydroxymethyl tetrahydroisoquinoline derivatives by the groups of Williams,<sup>84a</sup> Kaufman<sup>84b,c</sup> and Wipf<sup>84d</sup> during the synthesis of hydroxymethyl tetrahydroisoquinoline derivatives containing functionalities of MY336-a, tetrazomine and quinocarcin (and useful for the synthesis of quinocarcinamide) and in the construction of the AB ring system of tetrazomine. The homologative epoxidation followed by oxirane ring opening and modified Pomerantz–Fritsch cyclization strategies were also employed by the teams of Williams<sup>84a,e,f</sup> and Danishefsky<sup>84g,h</sup> for their total syntheses of tetrazomine and one of the saframycins.

## 6 Syntheses of Calycotomine from Preformed Isoquinolines

Reissert compounds have been used extensively as starting materials for the synthesis of isoquinoline and tetrahydroisoquinoline alkaloids<sup>85</sup> and have been demonstrated

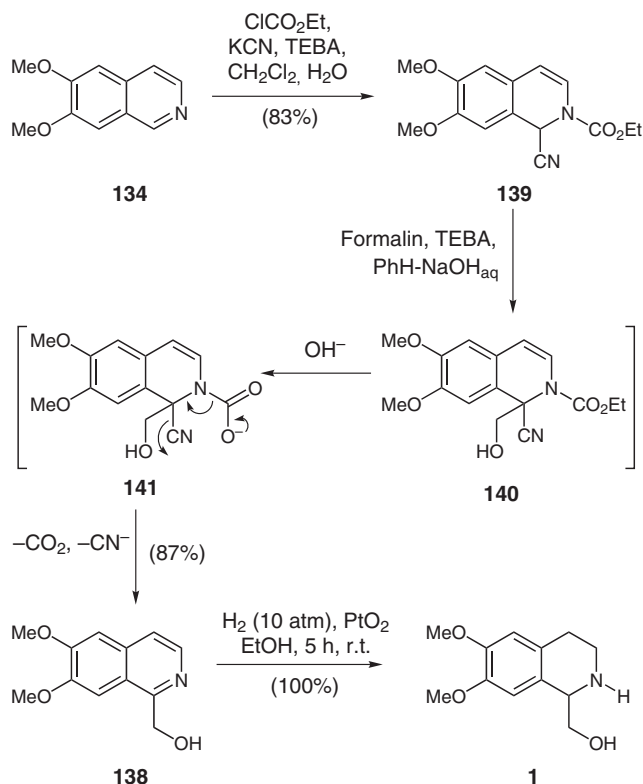
to condense with aldehydes.<sup>86</sup> These observations led Gibson and coworkers to design a facile entry to calycotomine employing 1-cyano-2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinoline (**136**) as key intermediate (Scheme 26).<sup>87</sup>

This was easily available either by Pomerantz–Fritsch cyclization of veratrylidene aminoacetal **135**<sup>88</sup> or by a Bischler–Napieralski cyclization of the formamide **132**, derived from homoveratrylamine (**29**), and subsequent dehydrogenation of the thus formed dihydroisoquinoline **133**.<sup>85a,89</sup> The resulting 6,7-dimethoxyisoquinoline (**134**) was then treated with benzoyl chloride and potassium cyanide.<sup>89</sup>

Treatment of the lithium anion of **136** with gaseous formaldehyde furnished benzoate **137**, which, after basic hydrolysis to **138** and subsequent catalytic hydrogenation, provided calycotomine in 44% overall yield from homoveratrylamine. The synthesis compared favorably with other previously reported racemic preparations of the natural product [Dubravkova<sup>30b</sup> (20%), Battersby (18%),<sup>30a</sup> Benington<sup>38</sup> (5%) and Chatterjee<sup>60</sup> (8%)]. Interestingly, the 6-demethyl analog of **138** was recently isolated from the marine sponge *Haliclone* sp.<sup>8c</sup>

The Polish group of Rozwadowska<sup>90</sup> prepared the related 6,7-dimethoxy-2-ethoxycarbonyl-1,2-dihydroquinolaldehyde nitrile (**139**) in 83% yield, by reaction of 6,7-dimethoxyisoquinoline (**134**) with ethyl chloroformate and potassium cyanide (Scheme 27).

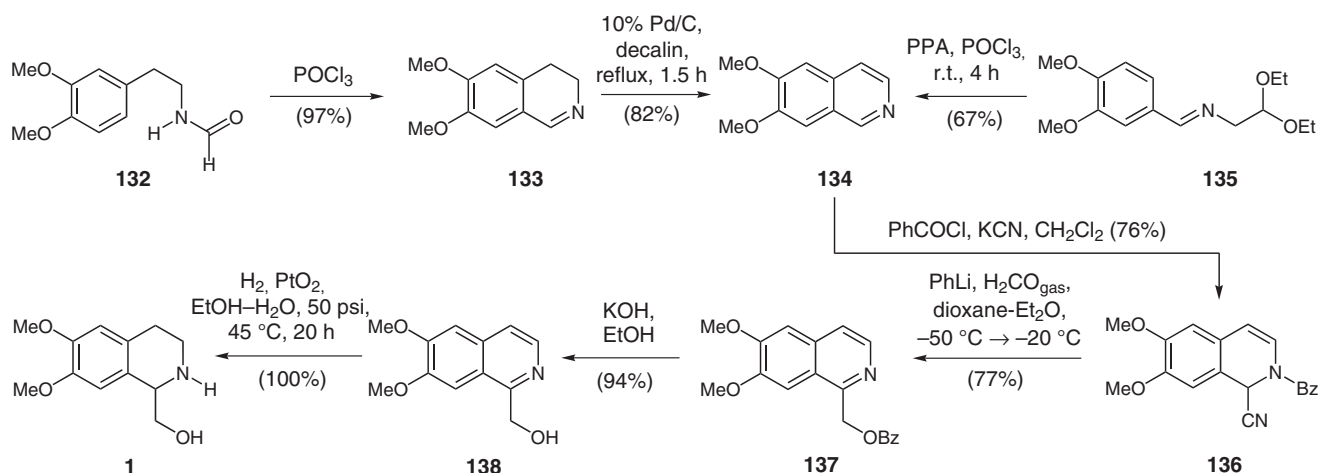
Reaction of the former with formalin, instead of gaseous formaldehyde, produced the 1-hydroxymethyl isoquinoline derivative **138** in 87% yield. Presumably, this occurred through the intermediacy of **140**, which, upon basic hydrolysis to **141**, triggers the loss of carbon dioxide and cyanide, with the resulting re-aromatization. Once submitted to catalytic hydrogenation with platinum oxide, **138** furnished calycotomine in quantitative yield. Other simple tetrahydroisoquinolines such as salsolidine (1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) and carnegine were obtained in a similar fashion.<sup>91</sup>



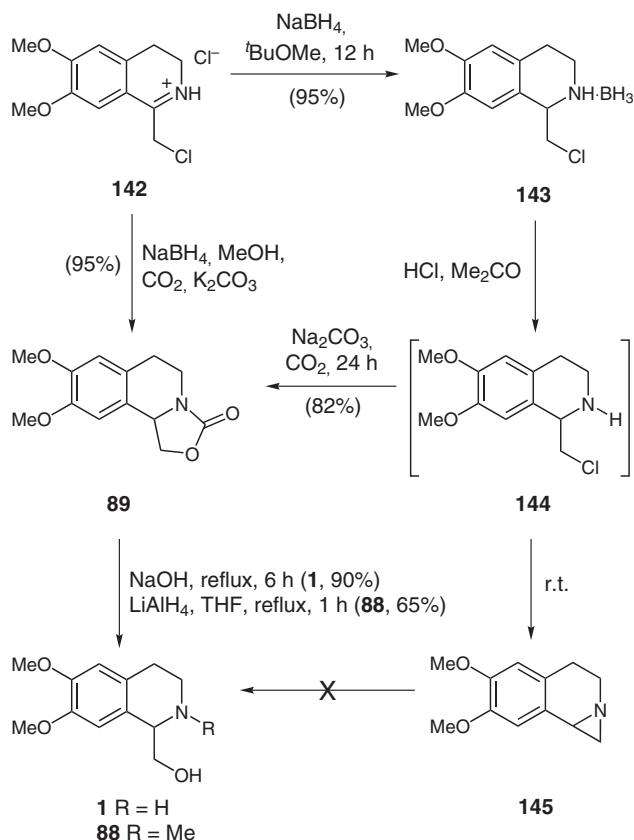
Scheme 27

Suau and co-workers prepared calycotomine, *N*-methylcalycotomine (**88**) and the related oxazolidinone **89** from 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium chloride (**142**).<sup>69b</sup> At 0 °C in the presence of  $\text{CO}_2$  and  $\text{K}_2\text{CO}_3$ , the  $\text{NaBH}_4$  reduction of the dihydroisoquinolinium salt in methanol furnished the 2-oxazolidinone **89** in almost quantitative yield. Further reduction of **89** with lithium aluminum hydride provided **88** in 65% yield, while basic hydrolysis of the oxazolidinone furnished 90% of calycotomine (Scheme 28).

Interestingly, reduction of **142** with sodium borohydride in *tert*-butyl methyl ether gave borane complex **143** which



Scheme 26



Scheme 28

also furnished oxazolidinone **89** in 78% overall yield. This pathway presumably involved the intermediacy of tetrahydroisoquinoline **144**, when the reaction was carried out under positive pressure of carbon dioxide. Carrying out the reduction at room temperature transformed intermediate **144** into aziridine **145** almost quantitatively, but this could not be converted into **88**.

## 7 Intramolecular Ring-Opening of a Chiral 1,3-Perhydrobenzoxazine

A total synthesis of calycotomine, leading to the *R*-enantiomer of the natural product as shown in Scheme 29, was recently reported by a Spanish team. This synthetic protocol was employed for the preparation of several related 1-substituted tetrahydroisoquinolines.<sup>92a</sup> Their strategy consisted in the intramolecular attack of an appropriately substituted aryl-aluminum species to the chiral 1,3-perhydrobenzoxazine **148**, derived from (–)-8-aminomethanol (**147**) and aldehyde **146** for the elaboration of the isoquinoline system, with compound **147** serving as chiral inductor and source of the nitrogen atom. The protocol constitutes another example of a type 1 isoquinoline synthesis according to Kametani's classification.

In this synthetic strategy, the aryl group was attached to the nitrogen of the *N,O*-acetal moiety of the 1,3-perhydrobenzoxazine through an ethylene tether. The elaboration of this synthetic intermediate was straightforward:

condensation of polysubstituted phenylacetaldehyde **146** with the chiral auxiliary was followed by reduction of the intermediate *N,O*-acetal **148** to amine **149**, which was further transformed into the *N,O*-heterocycle **150** in 59% yield upon heating with benzyloxymethyl acetate at 120 °C in a sealed tube.

Next, low temperature lithium-halogen exchange and transmetalation with diethylaluminum chloride provided an arylmetal which performed an intramolecular nucleophilic attack on C-2 of the *N,O*-heterocycle, forming the nitrogen-bearing ring of the tetrahydroisoquinoline **151**.

Finally, an efficient two-step removal of the chiral auxiliary led to **44** and then to **1**, by hydrogenolysis with Pearlman's catalyst, culminated the synthesis; this was performed by PCC-mediated oxidation of the alcohol **151** to the corresponding ketone **152** followed by a retro-Michael process, as depicted in **153**.

In this sequence, the stereochemistry of the final product was determined beforehand by the stereochemical outcome of the reaction leading to the key perhydrobenzoxazine **150**, in which the benzyloxymethyl substituent is equatorially oriented.<sup>92a</sup>

The key role of diethylaluminum chloride in the process leading to **151** was explained as shown in Scheme 30. The lithiated intermediate species **154** formed by lithium-halogen exchange of **150** with *tert*-butyl lithium is converted into the organoaluminum intermediate **155** by transmetalation with Et<sub>2</sub>AlCl. Next, intramolecular transfer of the aryl group to the *si*-face of the incipient iminium ion, from the aluminum atom, furnishes the aluminum species **157**, through the intermediacy of **156**. In turn, the former leads to **151** upon aqueous work-up.

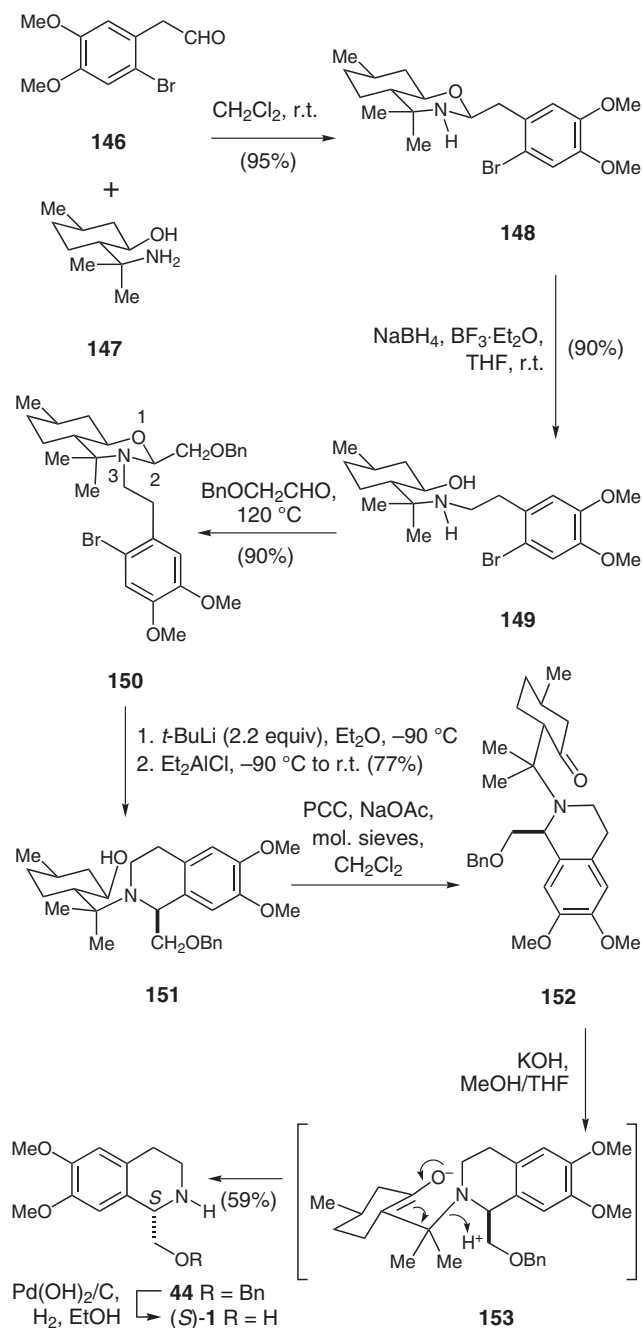
The stereochemical outcome of the intramolecular ring opening of the 1,3-perhydrobenzoxazine is similar to previous findings in related systems,<sup>53b</sup> while the better stereodiscrimination achieved with organoaluminum derivatives compared to the related organometallic species was ascribed to the comparative greater nucleophilic character of the former.<sup>93</sup>

The high selectivity observed is probably a consequence of the fact that transfer of the aryl group to the intermediate iminium moiety proceeds by synchronous intramolecular arylation in the early transition state **156**, while the aluminum is still complexed to the oxygen atom of the chiral auxiliary. In the case of related systems, when the less nucleophilic and less reactive organomagnesium species were employed, formation of minor amounts of the C-1 diastereomeric compound resulting from attack to the *re*-face was observed.

## 8 Conclusions

The various syntheses of calycotomine published during the last forty years are nothing but the result of the steady efforts of many investigations carried out by different synthetic organic chemists around the world, trying to chal-

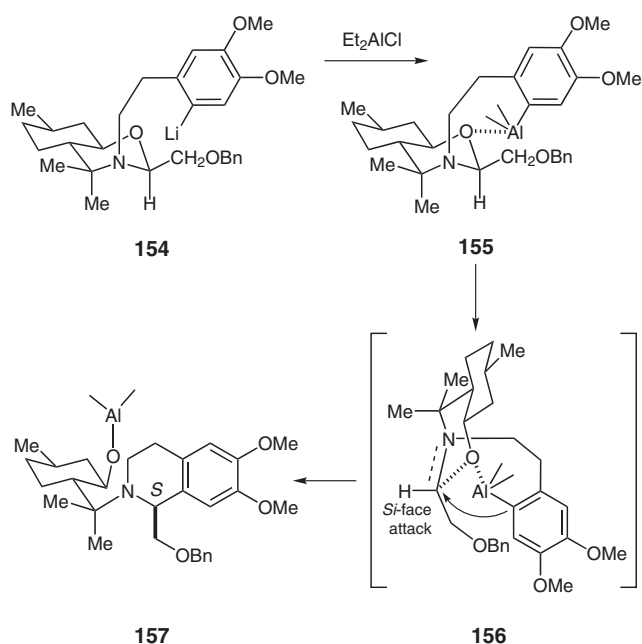




Scheme 29

lengthen the powers of chemical synthesis as well as their own capabilities and imagination.

The multiple syntheses of calycotomine have accompanied the remarkable progress in synthetic organic chemistry during the last four decades, evidencing the continuous evolution of reactions, reagents and synthetic strategies, towards the acquisition of the synthetic targets through more concise routes, in better chemical and optical yields, with improved atom economy and in increasingly imaginative ways.



Scheme 30

The traditional Bischler–Napieralski and Pictet–Spengler cyclizations, which originally furnished low to moderate yields of racemic calycotomine, were first turned into more efficient procedures and then slowly phased out by their most modern enantioselective versions, employing chiral starting materials, such as sugar derivatives and other optically active polyhydroxylated materials. In turn, these are now being superseded by enantioselective processes employing alternative and more powerful chiral auxiliaries or catalytic transformations with complex catalysts bearing optically active ligands. This transition is also a result of the outstanding developments in catalysis which have taken place during the last couple of decades.

Some of the synthetic procedures which have been explored and devised to carry out the synthesis of calycotomine have already found important applications in the conquering of other more demanding and often highly important targets, including complex natural products.

Therefore, in view of the continuous development of more sophisticated practical and powerful synthetic methods, it is expected that calycotomine will remain an interesting synthetic target and original total syntheses of calycotomine will continue to be disclosed in the near future.

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