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First Enantioselective Total Synthesis of (−)-Centrolobine

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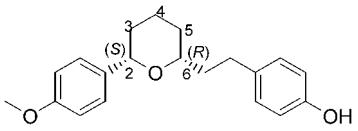
ABSTRACT



(-)-Centrolobine

The first enantioselective total synthesis of (−)-Centrolobine is described. The key reaction is the synthesis of the cis-disubstituted tetrahydropyran framework by intramolecular cyclization of the enantiopure hydroxyketone 3 with Et_3SiH and TMSOTf. The stereoselective reduction of the *β*-ketosulfoxide 4 is the source of chirality. Revision of the absolute configuration of (−)-Centrolobine is proposed.

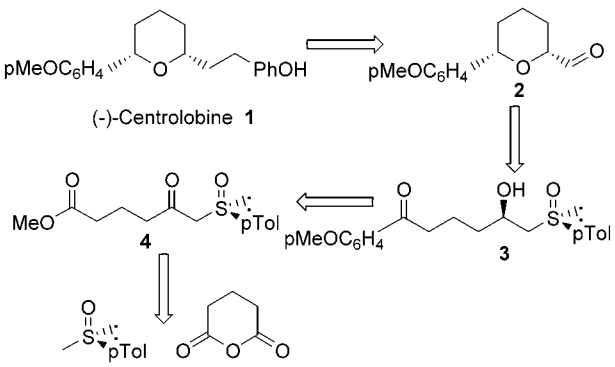
(−)-Centrolobine, 6[*β*(*p*-hydroxyphenyl)ethyl]-2-(*p*-methoxyphenyl)tetrahydropyran, is a crystalline substance isolated from the heartwood of *Centrolobium robustum*[1] and from the stem of *Brosinum potabile*[2] in the amazon forest. Although the basic structure was elucidated in 1964 by total synthesis of the racemic methyl ether,[1a,b] its absolute configuration has not been unequivocally established.

We report in this paper the first enantioselective synthesis of (−)-Centrolobine and propose a revision of its absolute configuration.

As shown in the retrosynthetic Scheme 1, our approach is based on the synthesis of aldehyde **2**, which could proceed from the intramolecular cyclization of the diastereomerically pure hydroxyketone **3**, readily available by stereoselective reduction of enantiopure *β*-keto sulfoxide **4**.

β-Ketosulfoxide (+)-(*R*)-**5** was prepared by condensation of glutaric anhydride and the carbanion of (+)-(*R*)-methyl *p*-tolyl sulfoxide (Scheme 2).[3] Esterification in the presence of dimethyl sulfate and potassium carbonate gave the ester **4** in 82% yield for the two steps. Although this sequence had already been reported,[4] we have improved the overall yield by working at −78 °C and modifying the esterifi-

Scheme 1



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(1) (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G.B. *Gazz. Chim. Ital*. **1964**, 287. (b) Galeffi, C.; Casinovi, C. G.; Marini-Bettòlo, G. B. *Gazz. Chim. Ital*. **1965**, 95. (c) Aragao Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869.

(2) Alcantara, A. F. de C.; Souza, M. R.; Piló-Veloso, D. *Fitoterapia* **2000**, *71*, 613.

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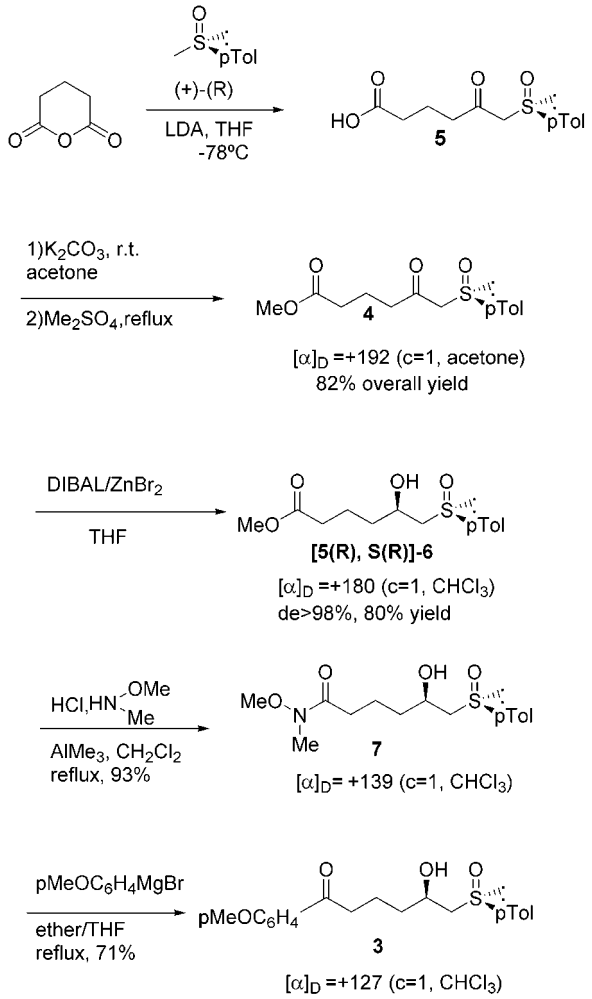
Scheme 2

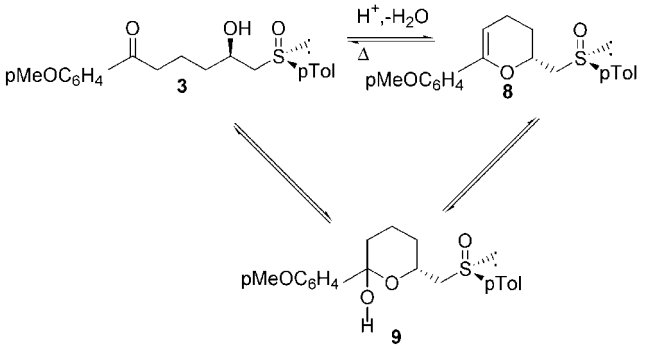


cation procedure. According to our previous results,[5] the reduction of the β-ketosulfoxide **4** with DIBAL/$ZnBr_2$ yielded [5(*R*),S(*R*)]-β-hydroxysulfoxide **6** in 80% yield and 98% de. The (*R*) configuration of the hydroxylic carbon was expected from the reaction mechanism already proposed[5d] and also from our ^{1}H NMR characterization of the product. From the numerous examples of reduction of β-ketosulfoxides already reported,[5b,c,f,6] we noticed that the nonequivalence of the methylene hydrogens α to the sulfoxide group is quite different in the two diastereomers: in the [5(*R*),S(*R*)] configuration, the $\Delta\nu$ value between these two hydrogens is ~40 Hz (38 Hz in **6**) and around 80 Hz in the [5(*S*),S(*R*)] epimers.[7] This correlation will be determinant in the final comparison with natural (−)-Centrolobine.

Without protection of the hydroxyl group, the methyl ester **6** was transformed into the *N*-methyl-*N*-methoxyamide (Weinreb amide)[8] **7** in 93% yield. The hydroxyketone **3** was then obtained in 71% yield by addition of *p*-methoxyphenylmagnesium bromide reagent to the Weinreb amide **7**.

With the hydroxyketone **3** in hand, we tried the cyclization under catalytic acid conditions (*p*-toluenesulfonic acid[9] or camphorsulfonic acid[10]) and obtained 50% of the starting hydroxyketone **3** and 50% of the dihydropyran **8** (Scheme 3). In these acidic conditions, it was impossible to isolate

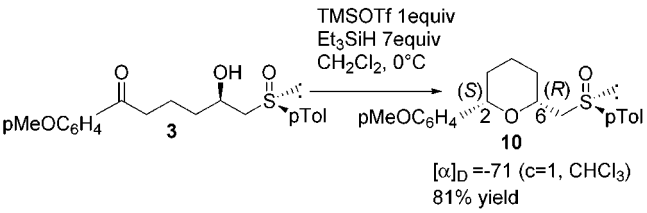
Scheme 3



the intermediate hemiketal **9**, which was dehydrated quickly to the very stable and highly conjugate dihydropyran **8**. It was not possible to improve the yield.

Following the work of Olah[11] and Nicolaou[12] who described the trimethylsilyl triflate catalyzed preparation of unsymmetrical ethers by reductive condensation of carbonyl compounds with alkoxysilanes, we treated the hydroxyketone **3** with an excess of Et_3SiH and TMSOTf in CH_2Cl_2 at 0 °C. After 15 min, we obtained in good yield (81%) the tetrahydropyran **10** with complete syn stereoselectivity (Scheme 4). The syn stereochemistry of **10** was assigned by

Scheme 4



^{1}H NMR spectroscopy on the basis of NOESY experiments. The configuration at the new stereogenic center must be

(3) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.
(4) Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreño M. C.; Garcia-Ruano, J. L. *J. Org. Chem.* **1991**, *56*, 2317.
(5) (a) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435. (b) Solladié, G.; Demailly, Greck, C. *J. Org. Chem.* **1985**, *50*, 1552. (c) Solladié, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912. (d) Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649. (e) Solladié, G.; Rubio, A.; Carreño M. C.; Garcia-Ruano, J. L. *Tetrahedron: Asymmetry*. **1990**, *1*, 187. (f) Carreño, M. C.; Garcia Ruano, J. L.; Martin, A.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120
(6) (a) Solladié, G.; Huser, N . *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 153. (b) Solladié, G.; Carreño, M. C. In *Organosulfur Chemistry: Synthetic Aspects*; Page, P. C. B., Ed.; Academic Press: New York, 1995; p 1. (c) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.
(7) Solladié, G.; Huser, N.; García Ruano, J. L.; Adrio, J.; Carreño, M. C.; Tito, A. *Tetrahedron Lett.* **1994**, *35*, 5297.
(8) Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 916.

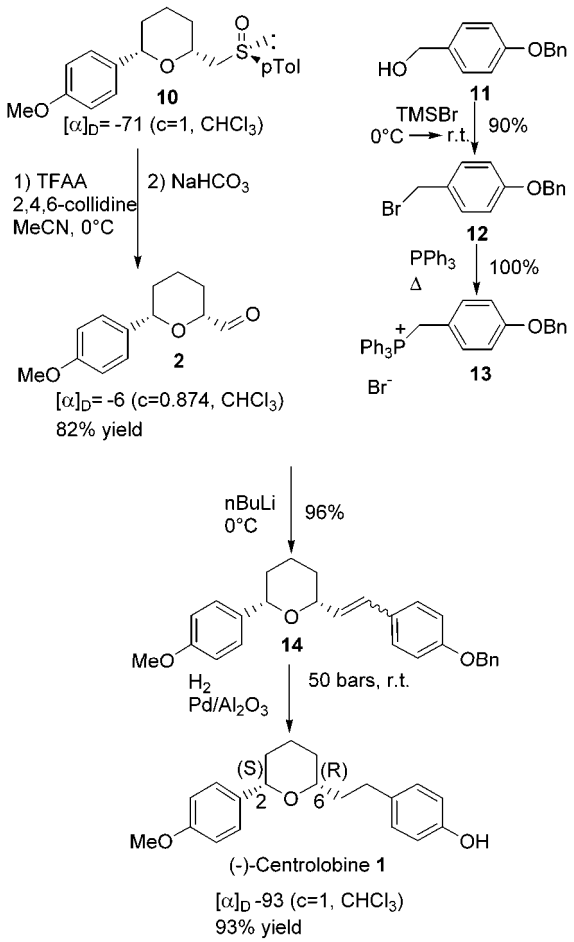
controlled by greater stability giving the syn diequatorial compound. Taking into account the absolute configuration of the precursor **3**, we assigned the [2(*S*),6(*R*),S(*R*)] configuration to the resulting sulfinyl tetrahydropyran **10**. The final comparison with the $[\alpha]_D$ of natural Centrolobine will indeed confirm this result.

To transform the sulfoxide **10** into the aldehyde **2** under very mild conditions, we used the classical TFAA-2,4,6-collidine Pummerer conditions.[13] Subsequent treatment of the Pummerer product with saturated aqueous sodium hydrogen carbonate afforded the aldehyde **2** in 82% yield (Scheme 5).

Compound **2** was then submitted to a Wittig reaction en route to (−)-Centrolobine. The necessary 4-benzyloxybenzyltriphenylphosphonium salt **13** was prepared from the commercially available 4-benzyloxybenzyl alcohol **11** in 95% overall yield.[14] The Wittig reaction between the salt **13** (2 equiv) and the aldehyde **2** was carried out in the presence of 2 equiv of BuLi to give the olefin **14** in excellent yield (96%).[15] Simultaneous reduction of the double bond and deprotection of the benzyl ether by catalytic hydrogenation afforded (−)-Centrolobine **1** in 93% yield.

^{1}H and ^{13}C NMR spectra, IR spectroscopic data, melting point (95 °C), and optical rotation ($[\alpha]_D$ −93, (*c* 1, $CHCl_3$)) of **1** were identical to those described for the natural product.[1,2] De Albuberque and co-workers[1c] proposed a [2(*R*),6(*S*)] absolute configuration for (−)-Centrolobine **1** on the basis of Brewster's empirical rules[16] on the correlation between molecular rotation and absolute configuration. We would like to revise the absolute configuration of (−)-Centrolobine **1** to [2(*S*),6(*R*)] on the basis of the absolute configuration of the β-hydroxysulfoxide [5(*R*),S(*R*)]-**6**, in turn established considering the well-known behavior of β-ketosulfoxide [S(*R*)]-**4** in the reductions with DIBAL/ZnX_2.

Scheme 5



In conclusion, we have reported the first efficient (nine steps and 26% overall yield from glutaric anhydride) asymmetric synthesis of (−)-Centrolobine **1**, which allowed the revision of its absolute configuration. Further application of this method to the asymmetric synthesis of differently substituted tetrahydropyran natural derivatives is in progress.

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(9) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, 604. (b) Chen, J.; Fletcher, M. T.; Kitching, W. *Tetrahedron: Asymmetry* **1995**, *6*, 967. (c) White, J. D.; Bolton, G. L.; Dantanarayana, A. P.; Fox, C. M. J.; Hiner, R. N.; Jackson, R. W.; Sakuma, K.; Warrier, U. S. *J. Am. Chem. Soc.* **1995**, *117*, 1908.

(10) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charrette, A. B.; Lautens, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2354.

(11) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314

(12) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.

(13) Sugihara, H.; Tanikaya, R.; Kaji, A. *Synthesis* **1978**, 881.

(14) Whalley, J. L.; Oldfield, M. F.; Botting, N. P. *Tetrahedron* **2000**, *56*, 455

(15) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 863.

(16) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5481.