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## AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-CASSIOL

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Abstract: An enantioselective total synthesis of (+)-cassiol 1 possessing potent antiulcerogenic activity has been accomplished by using an efficient construction methodology of the asymmetric quaternary carbon center via a highly diastereoselective intramolecular [3+2] dipolar cycloaddition reaction of the nitrile oxide 10 as a key step. Copyright © 1996 Elsevier Science Ltd

Cassiol  $1^1$  is an aglycone of the antiulcerogenic<sup>2</sup> natural product cassioside 2, which has been isolated from a hot water extract of Cinnamomi Cortex (the dried stem bark of *Cinnamomum cassia* Blume), and exhibits more potent antiulcer activity than 2. This compound contains a functionalized cyclohexenone moiety with the only existing asymmetric quaternary stereogenic center at C-4 and a 2-vinyl-1,3-diol appendage which is connected at the C-3 position (Figure 1). These structural features and the remarkable pharmacological activity have made it a challenging synthetic target, and five valuable contributions to the total synthesis<sup>3</sup> have appeared in recent years. In this paper, we wish to report an alternative total synthesis of (+)-cassiol employing a quaternary carbon construction methodology via a highly diastereoselective intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide.<sup>4</sup>



Prior to the synthesis, we envisioned that two contiguous chiral centers in the nitrile oxide 3 would constrain the conformation of the transition state of the [3+2] dipolar cycloaddition reaction to a more thermodynamically stable one, which leads to the diastereoselective formation of isoxazoline 4 or 5 with a quaternary stereogenic center at C-3a. To evaluate the absolute configuration and degree of stereoselectivity of the key step, we carried out the conformational search of the nitrile oxide 3 as a model for calculation. To

survey the transition states, we first generated a local minimized conformation including the special coordinates for the transition state of the [3+2] dipolar cycloaddition reaction<sup>5</sup>; then the Monte Carlo search<sup>6</sup> was carried out. Scheme 1 shows two of the lowest-energy transition structures T<sub>1</sub> and T<sub>2</sub> leading to the cycloadducts 4 and 5, respectively, and the energy difference is 15.6 kJ/mol. Thus, the calculations suggested that the *S*, *S*-derivative 3 should be chosen for the synthesis of (+)-cassiol and a high diastereoselectivity was expected even at relatively high temperature.



The preparation of oxime 9, a precursor of nitrile oxide 10, in optically active form and a key cycloaddition reaction are detailed in Scheme 2. Control of the relative and absolute stereochemistry is dependent upon the application of the asymmetric aldol methodology of Evans.<sup>7</sup> Aldol condensation of the boron enolate derived from acyl oxazolidinone 6 with 4-methylpent-4-enal<sup>8</sup> gave the single diastereomer 7 in 99% yield. Protection as the tetrahydropyranyl (THP) ether and reduction with LiAlH4 afforded primary alcohol  $\mathbf{8}$  in 60% yield for the two steps. Swern oxidation and reaction with hydroxylamine and sodium acetate gave oxime 9 in 89% yield. Treatment of 9 with 7% aqueous sodium hypochlorite<sup>9</sup> in dichloromethane for 8 h at room temperature provided isoxazoline 11 as the sole product in 88% yield via the nitrile oxide intermediate 10. Although the stereostructure of the cycloadduct could not be determined at this stage, it was suggested that the cycloaddition would proceed through a more favorable chair-like transition state 10, which was predicted by the above-mentioned calculations, to afford the requisite 3a-S isomer 11 shown in Scheme 2. The exact absolute configuration at the newly formed quaternary stereogenic center (C<sub>3a</sub>) could be established to be S by the observation of distinct NOE between the angular methyl protons and the axial methine proton at C-7 in alcohol 12, which was derived from 11 by acidic hydrolysis. The optical purity of 11 could be determined to be >99% ee by the analysis of <sup>1</sup>H-NMR of the corresponding MTPA ester 13 (Scheme 2).

With the requisite cyclohexanone skeleton containing the crucial quaternary stereogenic center in hand, we next turned our attention to the completion of the total synthesis. Reductive hydrolysis<sup>10</sup> of **11** with Raney nickel in the presence of trimethyl borate under an atmosphere of hydrogen afforded  $\beta$ -hydroxy ketone **14** in 88% yield. Protection as the t-butyldimethylsilyl ether and addition reaction of the vinyllithium reagent,<sup>3a</sup> generated *in situ* from vinylstannane **15** with n-butyllithium, resulted in the diastereoselective formation of tertiary allyl alcohol **16**<sup>11</sup> in 80% yield. Reaction of **16** with pyridinium *p*-toluenesulfonate (PPTS) in refluxing ethanol gave the deprotected triol, in which the 1,3-diol function was again protected as acetonide and the secondary alcohol was oxidized to give the functionalized cyclohexanone **17** in 48%

overall yield. Finally, treatment of 17 with hydrogen fluoride-pyridine complex<sup>3a</sup> produced, via deprotection and  $\beta$ -elimination, (+)-cassiol 1,  $[\alpha]_D$  +8.12° (lit.<sup>1</sup>, <sup>3a</sup>  $[\alpha]_D$  +8.63° ), whose spectral (IR and <sup>1</sup>H-NMR) properties were identical with those of an authentic material (Scheme 3).



Scheme 2. Reagents & Conditions: a, nBu2BOTf, <sup>i</sup>Pr2NEt, 4-methylpent-4-enal, CH2Cl2, -78 °C, 99%; b, 2,3-dihydropyran, PPTS, CH2Cl2, reflux; c, LiAIH4, THF, 60% for the 2 steps; d, Swern ox.; e, NH2OH•HCl, AcONa, MeOH, r.t., 89% for the 2 steps; f, 7% aq. NaOCl, CH2Cl2, r.t., 88%; g, PPTS, EtOH, reflux, 75%; h, (R)-MTPACl, Et3N, CH2Cl2, 89%.



Scheme 3. Reagents & Conditions: a, H<sub>2</sub> (2 Kg/cm<sup>2</sup>), Raney Ni, B(OMe)<sub>3</sub>, H<sub>2</sub>O, MeOH, r.t., 88%; b, TBSCl, imidazole, DMF, r.t., 97%; c, <sup>n</sup>BuLi, 15, THF, -78 °C - 0 °C, 80%; d, PPTS, EtOH, reflux; e, PPTS, 2, 2-dimethoxypropane, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; f, Swern ox., 48% for the 3 steps; g, HF-pyridine, CH<sub>3</sub>CN, pyridine, 73%.

In conclusion, we have accomplished an enantioselective total synthesis of (+)-cassiol 1 employing an efficient quaternary carbon construction methodology via an intramolecular [3+2] dipolar cycloaddition reaction, whose stereochemical outcome can be predicted by molecular mechanic calculations of the transition state model. Acknowledgement. We are grateful to Dr. Chikara Fukaya, Green Cross Corporation, for providing spectral (IR and <sup>1</sup>H-NMR) data of (+)-cassiol.

- **References and Notes** 
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- 11. The stereochemistry of a newly generated tertiary carbinol center in 16 was established as shown in Scheme 3 by the observation of NOE between one of the methylene protons ( $\delta$  3.56, d, J=9.3 Hz) of the hydroxymethyl moiety and an olefinic proton ( $\delta$  5.60, dd, J=18.0 and 5.3 Hz).

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