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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[2] 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[3] 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.[4]

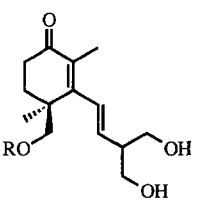
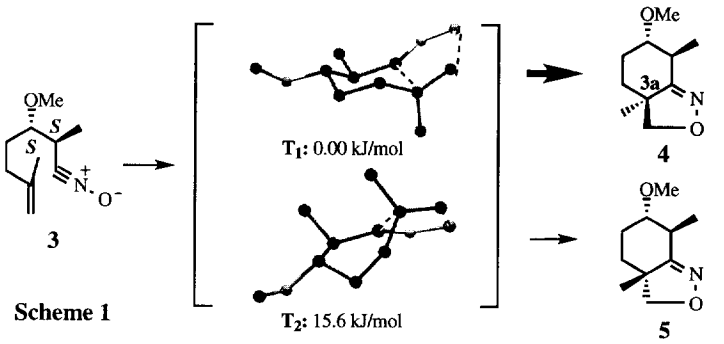


Figure 1

1 R=H: (+)-cassiol
2 R=β-D-glucopyranosyl: (-)-cassioside

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[5]; then the Monte Carlo search[6] was carried out. **Scheme 1** shows two of the lowest-energy transition structures $\mathbf{T_1}$ and $\mathbf{T_2}$ 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.

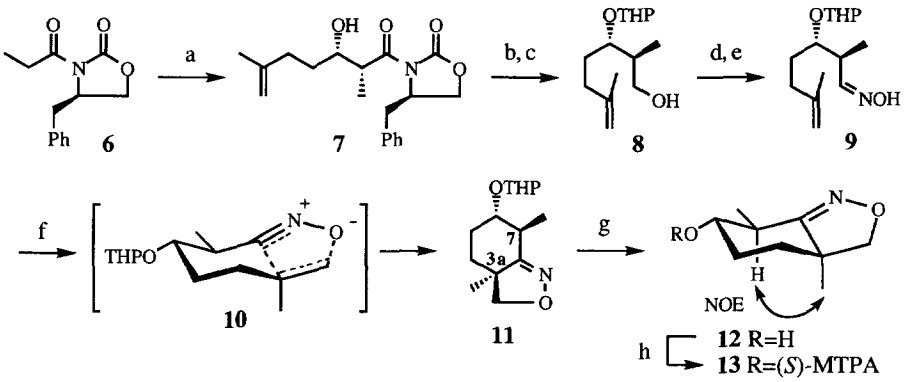


Scheme 1

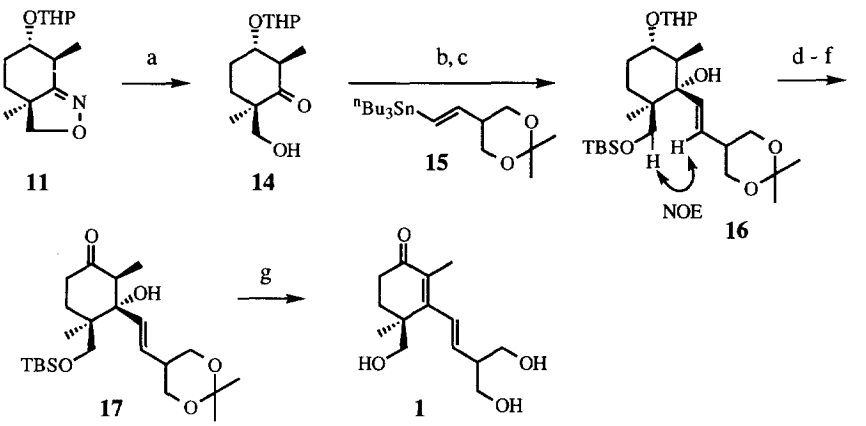
The preparation of oxime **9**, a precursor of nitrile oxide **10**, in optically active form and a key cycloaddition reaction are detailed in **Scheme 2**. Control of the relative and absolute stereochemistry is dependent upon the application of the asymmetric aldol methodology of Evans.[7] Aldol condensation of the boron enolate derived from acyl oxazolidinone **6** with 4-methylpent-4-enal[8] gave the single diastereomer **7** in 99% yield. Protection as the tetrahydropyranyl (THP) ether and reduction with $LiAlH_4$ afforded primary alcohol **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[9] 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_{3a}) 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 ^{1}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[10] of **11** with Raney nickel in the presence of trimethyl borate under an atmosphere of hydrogen afforded β-hydroxy ketone **14** in 88% yield. Protection as the t-butyldimethylsilyl ether and addition reaction of the vinyllithium reagent,[3a] generated *in situ* from vinylstannane **15** with n-butyllithium, resulted in the diastereoselective formation of tertiary allyl alcohol **16**[11] 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[3a] produced, via deprotection and β-elimination, (+)-cassiol **1**, $[\alpha]_D$ +8.12° (lit.[1, 3a] $[\alpha]_D$ +8.63°), whose spectral (IR and ^{1}H-NMR) properties were identical with those of an authentic material (**Scheme 3**).



Scheme 2. ***Reagents & Conditions:*** a, ^{n}Bu$_2$BOTf, ^{i}Pr$_2$NEt, 4-methylpent-4-enal, CH_2Cl_2, -78 °C, 99%; b, 2,3-dihydropyran, PPTS, CH_2Cl_2, reflux; c, $LiAlH_4$, THF, 60% for the 2 steps; d, Swern ox.; e, NH_2OH•HCl, AcONa, MeOH, r.t., 89% for the 2 steps; f, 7% aq. NaOCl, CH_2Cl_2, r.t., 88%; g, PPTS, EtOH, reflux, 75%; h, (*R*)-MTPACl, Et_3N, CH_2Cl_2, 89%.



Scheme 3. ***Reagents & Conditions:*** a, H_2 (2 Kg/cm^2), Raney Ni, $B(OMe)_3$, H_2O, MeOH, r.t., 88%; b, TBSCl, imidazole, DMF, r.t., 97%; c, ^{n}BuLi, **15**, THF, -78 °C - 0 °C, 80%; d, PPTS, EtOH, reflux; e, PPTS, 2, 2-dimethoxypropane, CH_2Cl_2, r.t.; f, Swern ox., 48% for the 3 steps; g, HF-pyridine, CH_3CN, 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.

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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 (δ 3.56, d, *J*=9.3 Hz) of the hydroxymethyl moiety and an olefinic proton (δ 5.60, dd, *J*=18.0 and 5.3 Hz).

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