ENANTIOCONTROLLED SYNTHESIS OF THE FUNCTIONALIZED *cis*-DECALIN[†]

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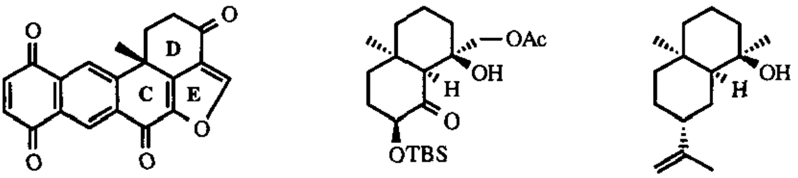
Abstract - An enantioselective synthesis of the functionalized *cis*-decalin (**2**) has been accomplished employing a highly diastereoselective intramolecular [3+2] dipolar cycloaddition reaction of the optically active nitrile oxide (**16**) as the key step.

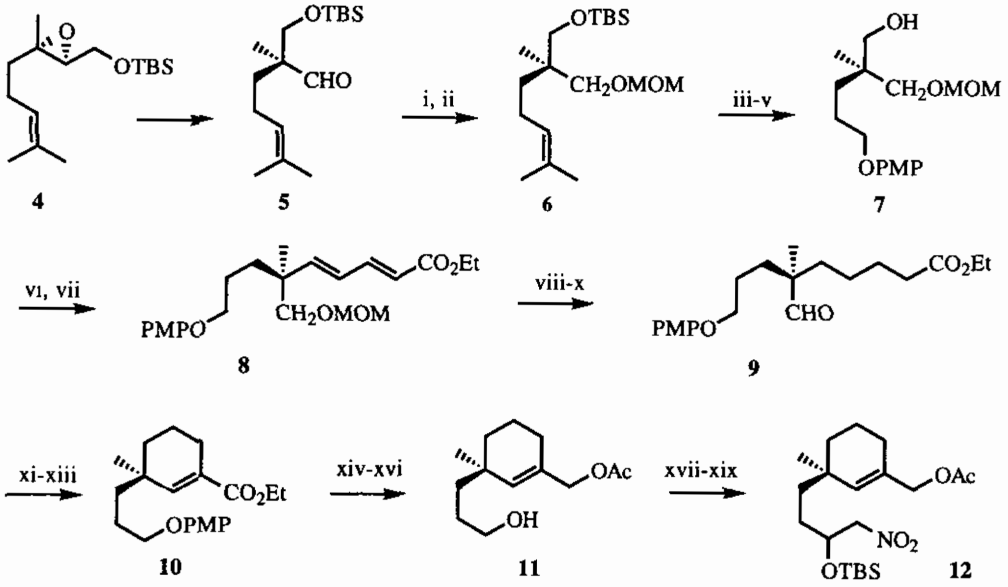
During the course of our investigation directed towards an asymmetric synthesis of the biologically active marine natural product halenaquinone (**1**),[1] we intended to explore an efficient and enantioselective route to the functionalized *cis*-decalin (**2**), which involves a quaternary stereogenic center at the angular position and would be transformed to the CDE ring segment of *ent*-**1** by using our fused furan construction methodology.[2] It was envisioned that the development of a chiral route to **2** would also be valuable for the asymmetric access to biologically interesting natural products having a *cis*-decalin moiety, e.g., amiteol (**3**)[3] which has been found in the defensive secretion of terminate soldiers. In this paper, we report an enantiocontrolled synthesis of **2** employing a highly diastereoselective intramolecular [3+2] dipolar cycloaddition reaction of the optically active nitrile oxide (**16**) as the key step.



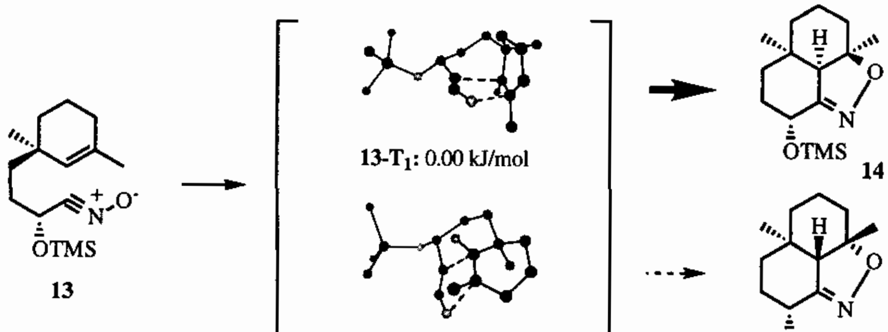
halenaquinone (1) **2** **amiteol (3)**

Figure 1

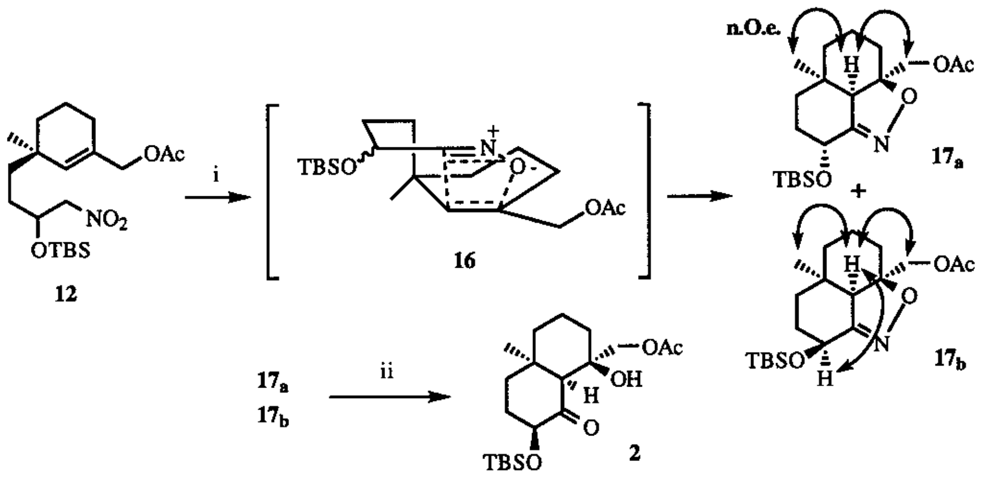
An asymmetric quaternary stereogenic center which exists in **2** was constructed employing the organoaluminum-promoted rearrangement developed by Yamamoto.[4] Thus, treatment of the optically active epoxy silyl ether (**4**), prepared from the Sharpless asymmetric epoxidation of geraniol using L-(+)-diethyl tartrate followed by silylation, with methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) provided the *S*-aldehyde (**5**) in 97% yield and 95% ee. Reduction of **5** with sodium borohydride ($NaBH_4$) followed by protection of the primary hydroxy group as the methoxymethyl (MOM) ether gave **6** in 95% yield. Sequential ozonolysis, reductive workup with $NaBH_4$, protection of the resulting primary hydroxy moiety as a *p*-methoxyphenyl (PMP) ether by using the Mitsunobu conditions and deprotection of the silyl ether produced the alcohol (**7**) in 88% overall yield from **6**. Carbon-chain elongation was effected by Swern oxidation of **7** followed by the Horner-Emmons olefination to give the dienyl ester (**8**), which was converted into the aldehyde (**9**), the substrate for the intramolecular Claisen condensation, by sequential catalytic hydrogenation, acid hydrolysis and Swern oxidation in good overall yield. The cyclization was achieved efficiently by treatment of **9** with lithium hexamethyldisilazide[5] to give the β-hydroxy ester, which was dehydrated *via* the acetate to afford **10** in 79% yield for the three steps. Reduction of **10** with diisobutylaluminum hydride, protection of the primary hydroxy group as the acetate and deprotection of the PMP ether with ammonium cerium nitrate provided **11**, which was then subjected to sequential oxidation, addition of nitromethane and silylation to produce **12** as an inseparable mixture of two diastereoisomers in good overall yield. (Scheme 1) With the successful preparation of **12** in hand, we were ready to tackle the crucial cycloaddition step. To evaluate the absolute configuration and degree of diastereoselectivity of the key step, we carried out the conformational search of the nitrile oxide (**13**) as a model for calculation.[6] Following the precedented example,[7] the calculation was carried out and two of the lowest energy transition structures (**13-T$_1$**) and (**13-T$_2$**), leading to the cycloadducts (**14**) and (**15**), are shown in Scheme 2. The energy difference is 34.9 kJ/mol and highly diastereoselective formation of the *cis*-fused cycloadduct (**14**) was expected even at relatively high temperature. On exposure of **12** to *p*-chlorophenyl isocyanate and triethylamine[8] in benzene at room temperature, the expected intramolecular [3+2] dipolar cycloaddition occurred smoothly *via* the transition state (**16**) to provide the isoxazolines (**17a,b**), which were easily separable by SiO_2 column chromatography, in 48% and 42% yields, respectively. The structures of both products were determined mainly by ^1H-NMR spectra and their n.O.e. experiments as shown in Scheme 3. Finally, the isoxazolines (**17a,b**) thus obtained were independently treated under reductive hydrolysis conditions to give, unexpectedly, the same siloxy ketone (**2**) in 36% and 62% yields, respectively. The structure of **2** was established by ^1H-NMR. Using one-dimensional n.O.e., the configuration at the siloxy-bearing carbon center was assigned to be *S* as summarized in Figure 2 in which signal enhancements are indicated by arrows. From these facts, it was confirmed that **2** existed not in the nonsteroidal but in the steroidal conformation. In summary, the functionalized *cis*-decalin (**2**) has successfully been synthesized in an enantiomerically pure form by means of a highly diastereoselective intramolecular [3+2] dipolar cycloaddition reaction of the chiral nitrile oxide, which was efficiently derived from geraniol.



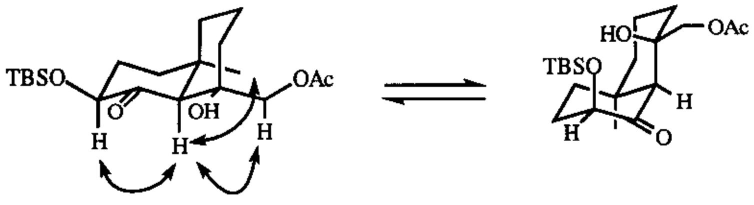
Scheme 1. ***Reagents and Conditions*:** i, $NaBH_4$, EtOH, 0 °C, 98%; ii, MOMCl, $^iPr_2NEt$, 4-DMAP, CH_2Cl_2, rt, 97%; iii, O_3, CH_2Cl_2, -78 °C then $NaBH_4$, CH_2Cl_2, rt, 88%; iv, *p*-methoxyphenol, Ph_3P, $^iPrO_2CN{=}NCO_2{}^iPr$, THF, rt; v, $^nBu_4NF$, THF, rt, 100% for 2 steps; vi, Swern ox., CH_2Cl_2, -78 °C - rt; vii, $(EtO)_2POCH_2CH{=}CHCO_2Et$, NaH, DME, rt, 79% for 2 steps; viii, H_2, Pd-C, EtOH, rt, 95%; ix, HCl, EtOH, 60 °C, 85%; x, Swern ox., CH_2Cl_2, -78 °C - rt, 91%; xi, $LiN(TMS)_2$, HMPA, THF, -78 °C, 79%; xii, Ac_2O, pyridine, 4-DMAP, rt; xiii, DBU, 110 °C, 100% for 2 steps; xiv, $^iBu_2AlH$, THF, -78 °C, 98%; xv, Ac_2O, pyridine, 4-DMAP, rt, 97%; xvi, $(NH_4)_2Ce(NO_3)_6$, MeCN:H_2O=4:1, 0 °C; xvii, Swern ox., -78 °C - rt, 75% for 2 steps; xviii, $MeNO_2$, KF, 18-Crown-6, ^iPrOH, rt; xix, TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 73% for 2 steps.



Scheme 2



Scheme 3. ***Reagents and Conditions*****:** i, *p*-ClC_6H_4NCO, Et_3N, benzene, rt, 90%.
ii, H_2 (2 Kg/cm^2), Raney Ni, $(MeO)_3B$, MeOH:H_2O=10:1, 36% from **15**$_a$, 62% from **15**$_b$.



2-steroidal **Figure 2** **2-nonsteroidal**

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[†] Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

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