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Studies on the Enantioselective Deprotonation of 2,4-Dimethylbicyclo[3.2.1]octan-3-one

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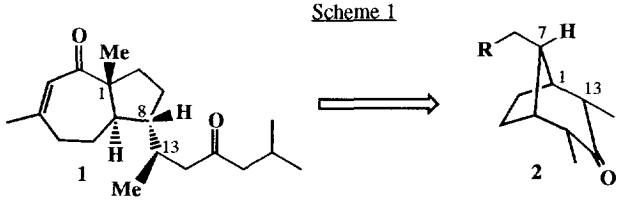
Abstract: The desymmetrization of 2,4-dimethylbicyclo[3.2.1]octan-3-one by enantioselective deprotonation with a variety of chiral amine bases has been studied. The enantioselectivities ranged from 5% for camphor derived amine **11** to 85% for Koga's base **13**.

The ready availability of chiral materials is vital to modern organic synthesis and much effort has been expended in developing new methodology to meet this requirement.[1] As a result, a number of diastereoselective processes have become available, but by contrast only a few good general chemical methods for efficient intermolecular transfer of chirality have been developed.[2] One such method beginning to emerge is the use of chiral lithium amides for the enantioselective deprotonation of meso ketones.[3]

In a project directed towards the total synthesis of (–)-Reiswigin A[4] (**1**) we had need for a method that would desymmetrize meso bicyclo[3.2.1]octan-3-one adduct **2** (scheme 1; the numbered carbons in **2** correspond to their eventual position in the natural product). Although efficient desymmetrization of oxa- and azabicyclo[3.2.1]ketones has been elegantly demonstrated by Simpkins[5] and Majewski,[6] the corresponding

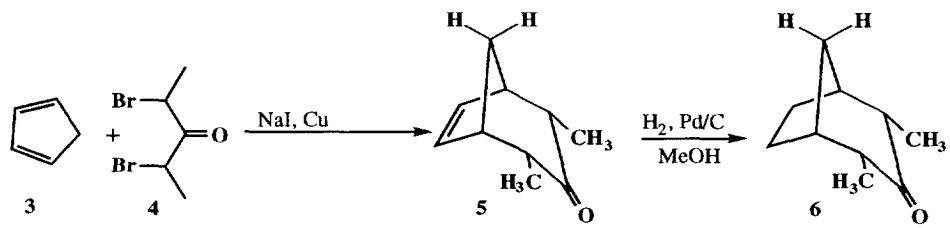
Scheme 1



carbocyclic analogue has not been investigated. Due to the general lack of understanding of the crucial transition state geometry, as well as the role of other factors such as solvent, temperature and additives (HMPA, LiCl), it is unfortunately not easy to predict the usefulness of this strategy. With this in mind we developed a model of our bicyclo[3.2.1]ketone to investigate the potential of this approach for the synthesis of (–)-Reiswigin A.

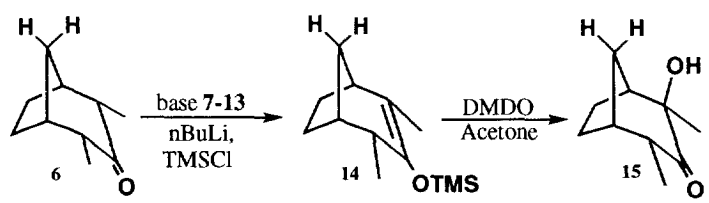
Construction of the model compound is outlined in Scheme 2. Efficient [4+3]-cycloaddition according to the procedure developed by Hoffmann,[7] followed by hydrogenation generated ketone **6** in 70% overall yield as a 5:1 mixture of α,α and β,β-isomers. Contrary to published reports,[7] these isomers could be completely

Scheme 2



separated by careful SiO_2 column chromatography (17:1 hexane/ethyl acetate as eluant). With stereochemically pure ketone **6** in hand, the stage was now set to investigate the deprotonation. Initially we reacted **6** with lithium diisopropylamide (LDA), an achiral base, to elaborate a method for measuring the enantiomeric excess (ee) of the reaction. The resulting enolate was treated with excess chlorotrimethylsilane to generate the TMS enol ether (scheme 3). Unfortunately, we could not find a chiral shift reagent that would allow us to analyze the ee's of **14**; therefore we looked for other derivatives which would permit analysis in this way. Oxidation of enol ether **14** under a variety of conditions met with no success (OsO_4, $KMnO_4$ and mCPBA); however, treatment of **14** with freshly prepared dimethyldioxirane[8] (DMDO) furnished α-hydroxy ketone **15** in 72% yield as a single stereoisomer. Addition of 35 mole % of tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III) derivative [Eu(hfc)$_3$] to **15** caused baseline separation of the methyl doublets in the two enantiomers, thus allowing easy calculation of the ee's. The stereochemistry of **15** has not been rigorously determined, but extensive noe studies suggest it to be as shown.[9]

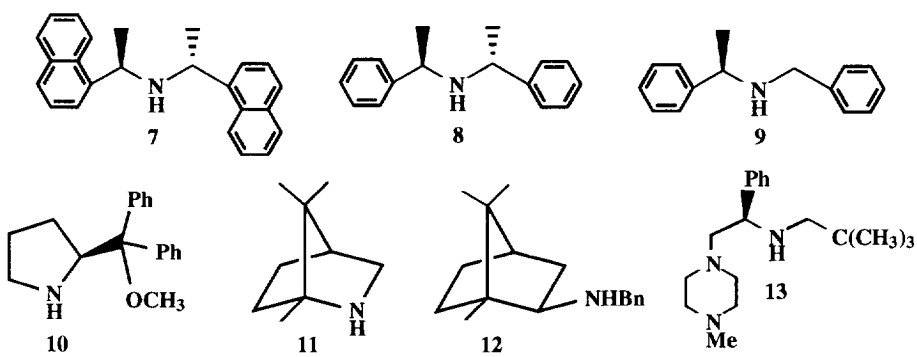
Scheme 3



Although numerous chiral amine bases exist, we decided to investigate those which have shown the most promise in the enantioselective deprotonation of other cyclic ketones (**8**,[10] **9**,[10] **12**[10] and **13**,[11] Figure 1), as well as some that we have developed in our laboratories (**7**,[12] **10**[13] and **11**,[14] Figure 1). Thus, treatment of ketone **6** with the chiral lithium amides derived from amines **7-13**, and either using Corey's internal quench,[15] or Simpkins's external quench,[16] TMS-enol ether **14** was cleanly produced in 62%-95% isolated yield.[17] Oxidation with DMDO followed by product isolation allowed for measurement of the enantiomeric excesses, and

the results are presented in Table 1. All the amides studied produced preferentially the levorotatory enantiomer with excesses ranging from poor (5% for **10** and **11**) to good (85% for **13**). Although the absolute configuration of enol ether **14** has not been unambiguously proven, it is assumed to be as shown based on similar studies performed by Koga[11] and Simpkins.[10] It should be noted from the table that there is in some

Figure 1



instances a dramatic difference in the observed ee between the internal and external quenches (entry 6). Simpkins and others have noted this trend and attribute it to LiCl, generated as the internal quench begins, modifying the selectivity of the lithium amide, possibly by forming mixed aggregrates.[16] The reasons for the

Table 1: Enantioselective deprotonation of ketone **6** with chiral lithium amides derived from amines **7-13**. No external additives such as LiCl or HMPA were used in any of the examples. The yield and ee refer to compound **14** in each case.

Entry	CLAMB	Yield (%)	e.e. (internal)	e.e. (external)
1	7	95%	45%	30%
2	8	96%	23%	15%
3	9	89%	10%	10%
4	10	80%	5%	-
5	11	95%	5%	5%
6	12	75%	76%	46%
7	13	62%	85%	-

low inductions observed when using bases **7-11** are not readily obvious, especially considering the utility and success of some of these types of reagents in other studies of enantioselectivity.

In conclusion, we have demonstrated that moderate to good levels of asymmetric induction can be achieved in the enantioselective deprotonation of 2,4-dimethylbicyclo[3.2.1]octan-3-one. Efforts to improve the ee's (i.e. adding LiCl or HMPA, lower temperature, and using other chiral amine bases currently being developed by us), as well as utilizing this strategy towards the total synthesis of (–)-Reiswigin A are currently being pursued.

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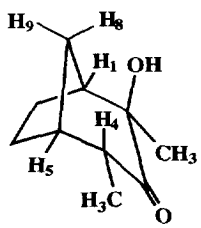
9. Some of the noe studies on hydroxy ketone **15** are listed below. No enhancements were observed with either of the methyl groups when H_8 was irradiated, or with H_8 when either of the methyl groups were irradiated. Based on these results we assigned the stereochemistry of **15** as shown.



Irradiate H_4: H_4-H_8 2.9%
H_4-H_5 2.1%
H_4-C_4 Methyl 4.9%

Irradiate H_8: H_8-H_4 3.7%
H_8-H_1 0.7%
H_8-H_5 1.1%
H_8-H_9 13.5%

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17. **Typical experimental conditions for internal quench:** In a 25 mL flame dried RBF was placed 2.1 mmol of amine in 7.5 mL of THF. The solution was cooled to $^{-}78^{o}$C and 2 mmol of 2.5M nBuLi was added dropwise over 1 minute. After complete addition and stirring for 20 minutes the cold bath was removed and the reaction mixture was allowed to warm to RT. The solution was then recooled to $^{-}78^{o}$C and 5 mmol of TMSCl was added in one portion followed by dropwise addition of **6** (1 mmol) in 2 mL of THF over 3 minutes. After stirring at this temperature for 30 minutes 1 mL of triethylamine was added and the solution was diluted with Et_2O and filtered through a pad of Celite. Evaporation and SiO_2 chromatography (30:1 hexanes:ethyl acetate) produced enol ether **14** as a colorless oil. ^{1}H NMR (200 MHz), δ: 0.15 (s, 9H), 0.98 (d, J=2.3Hz, 3H), 1.54 (d, J=2.3 Hz, 3H), 1.37-1.83 (m, 6H), 2.12-2.27 (m, 2H), 2.46-2.62 (m, 1H); IR (cm^{-1}): 2960 (s), 2906 (s), 2862 (s), 1672 (s), 1197 (s), 909 (s), 470 (s); HRMS: $C_{13}H_{24}OSi_{calc.}$ 224.1597, $C_{13}H_{24}OSi_{obs.}$ 224.1552; $[\alpha]_D$=$^{-}$20.6 (c=1.0, CH_2Cl_2; ee=85%).

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