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Birch Reduction and Reduction-Alkylations of 3,4-Dihydro-3-methyl-8-phenylisocoumarin

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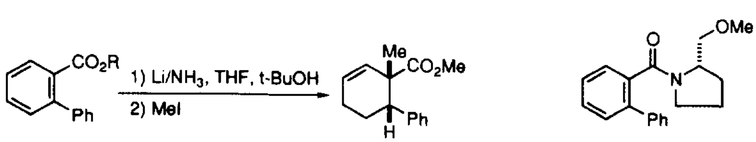
Abstract: Birch reduction and reduction-alkylations of **4** provide 3-methyl-8-phenyl-3,4,5,6,7,8-hexahydroisocoumarin **6** (88% yield) and a series of 8a-substituted-3-methyl-8-phenyl-3,4,6,7,8,8a-hexahydroisocoumarins **5a-d** (84-89%). Conversions of **5a** and **6** to cyclohexenones **12** and **13**, and **6** to butadiene carboxylic acid **14** also are described.

The first report of Birch reduction-alkylations of biarylcarboxylic acid derivatives appeared in 1988.[1] Reduction of methyl 2-phenylbenzoate (**1a**) with lithium in NH_3/THF in the presence of 3 equiv of t-BuOH followed by treatment of the resulting lithium enolate with methyl iodide gave a single C(3)-methylated tetrahydrobenzoic acid ester **2** in 90% yield. The chiral benzamide **3** and a series of alkylation reagents provided analogous tetrahydrobenzamides with high diastereoselectivities (~10:1); product yields ranged from 40-85%. In this paper, we report the highly diastereoselective Birch reduction and reduction-alkylations of chiral 3,4-dihydro-3-methyl-8-phenylisocoumarin (**4**)[2] to give hexahydroisocoumarins with excellent potential for further synthetic conversions. It is noteworthy that stereocontrol at C(8) is the result of 1,5-intraannular chirality transfer, a strategy that is relatively rare in asymmetric organic synthesis.[3]



1a, R = Me
b, R = H

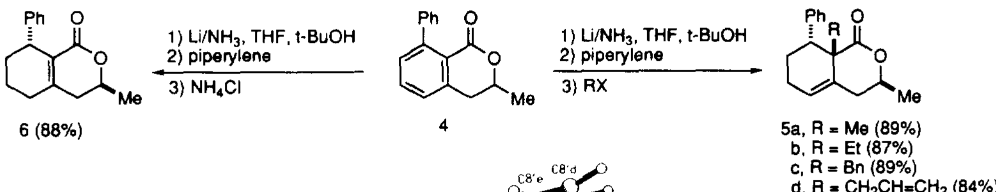
2 (90%)

3

A solution of **4** (0.2 mmol) and t-BuOH (3.5 equiv) in THF was slowly added (5 min) to a stirred solution of Li (10 equiv) in NH_3 cooled to -78 °C. After 2 h at -78 °C, piperylene was added until the blue coloration disappeared. A solution of the alkylation reagent (2-4 equiv) in THF was added and after an additional 2 h at -78 °C, the reaction was quenched with 1N NH_4Cl solution. Under these conditions, the 8a-substituted hexahydroisocoumarins **5a-d** were obtained in yields ranging from 84 to 89% as mixtures (~14:1) of two diastereomers **5** and **11**.[4] A single-crystal X-ray structure determination for **5c** provided the molecular structure shown in Figure 1.

Direct quenching of the enolate with solid NH_4Cl at -78 °C gave 3-methyl-8-phenyl-3,4,5,6,7,8-hexahydroisocoumarin as a mixture of two diastereomers (14:1) in 88% yield. The major diastereomer **6** was separated by careful chromatography on silica gel and fully characterized, but the minor isomer **10** could not be obtained free of **6**.

A pronounced dependence of stereocontrol at C(8) on the structure of the alcohol (ROH) present during Birch reduction is shown in Table I. It is assumed that mixtures of enolates **8** and **9**, diastereomeric at C(8), are generated from Birch reductions of **4** (Scheme I). The stereoselectivity for formation of **6** and **10** ranged from 5:1 to 14:1, depending on the structure of ROH, when the enolate mixtures were quenched with NH_4Cl. However, when the same enolate mixtures were alkylated with MeI, the stereoselectivity for formation of **5a** and **11a** was invariant at 14:1. A significantly higher selectivity for formation of **5a** and **11a** (30:1) was observed when the alkylation reaction was quenched (NH_4Cl) before alkylation was complete; in this case, the amount of **10** observed in the reaction mixture far exceeded that of **6**.



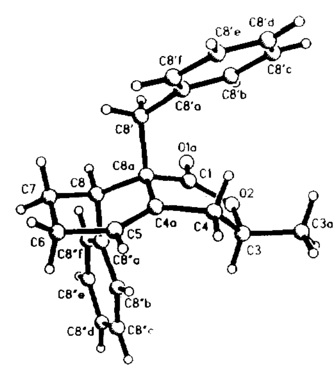


Figure 1. Molecular structure of **5c**

These data demonstrate that there is a pathway available for interconversion of enolates **8** and **9**. The most reasonable mechanism for interconversion is that **8** and **9** are in equilibrium with the dianion **7** as shown in Scheme I. Remarkably (and fortuitously with regard to mechanistic understanding) the positions of the equilibria appear to depend on the structure of the alcohols present in the reaction mixtures. It is assumed that protonations of the enolate mixtures with added NH_4Cl are rapid and occur under kinetic control. Thus, the distributions of **6** and **10** shown in Table I may reflect the distributions of enolates **8** and **9** under the indicated reaction conditions. Alkylations of **8** and **9** also are under kinetic control, but the slower reaction rates relative to protonation allow discrimination ($k_1 > k_2$) between **8** and **9** and the enhancement of diastereoselectivity at C(8) in the presence of MeOH or i-PrOH. That k_1 is greater than k_2 is supported by entry 4 in Table I showing a higher selectivity of 30:1 for formation of **5a** and **11a** in the presence of t-BuOH before alkylation has proceeded to completion.

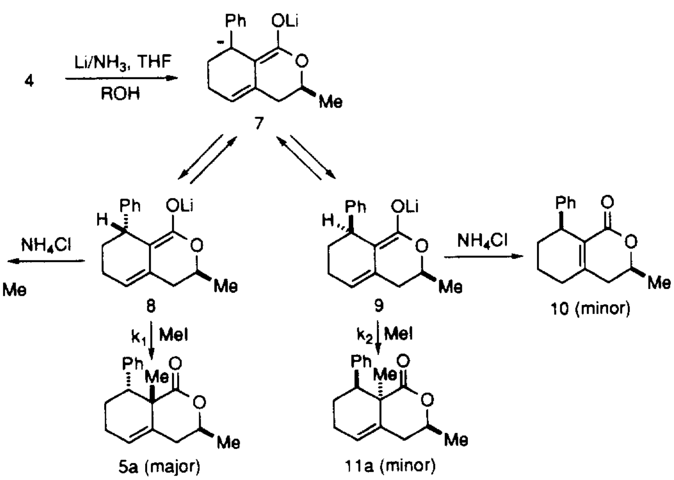
C(8) alkylation products from reduction-alkylation of **4** have not been observed suggesting that substantial quantities of dianion **7** probably are not present in the equilibrium shown in Scheme I. This is not surprising because the C(8) carbanion is not well positioned for delocalization to the phenyl substituent or the π-system of the enolate; consider C(8) in Figure 1.

Table I. Effect of Alcohol (ROH) on the Birch Reduction of **4**[a]

entry	ROH[b]	Quench with NH_4Cl; distribution of **6** and **10**[c]	Quench with MeI; distribution of **5a** and **11a**[d]
1	MeOH	5.0:1	14:1
2	i-PrOH	5.6:1	14:1
3	t-BuOH	14:1	14:1
4	t-BuOH	-----	30:1[e]

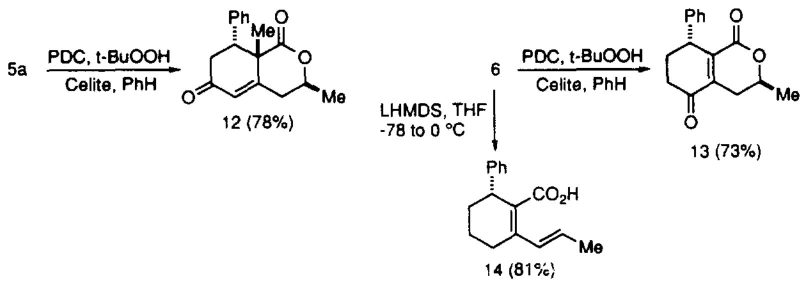
[a]Determined by ^1H NMR analysis. [b]3.5 equiv of ROH in each reaction. [c]Product yields for all cases ~88%. [d]Product yields ~89% for all cases except entry 4. [e]Shorter reaction period for alkylation compared to entry 3; **10** was the major by-product under these reaction conditions.

Scheme I



Products from Birch reduction and reduction-alkylation of **4** undergo useful synthetic transformations. Oxidation of **5a** with PDC and t-BuOOH[5] gave cyclohexenone **12** in 78% yield; oxidation of **6** gave cyclohexenone **13** (73%). It is noteworthy that competing oxidation at the alternative allylic position C(4) in **5a** and **6** was not observed. Treatment of **6** with lithium hexamethyldisilazide (LHMDS) in THF gave the butadiene carboxylic acid **14** (81%).[6]

Isocoumarin **4** was prepared by alkylation of the C(6) anion of the oxazoline derivative of 2-phenylbenzoic acid (**1b**).[2] Although racemic propylene oxide was utilized in the present study, non-racemic propylene oxide is available.[7] Other chiral terminal epoxides have been obtained with a high degree of enantiomeric purity by asymmetric dihydroxylation[8] and enzymatic epoxidation of terminal olefins.[9] Biaryl construction particularly by aryl coupling reactions[10] will provide analogues of **4** with virtually any substitution on the aromatic rings. The application of chemistry described in this note to problems in asymmetric organic synthesis is under active investigation.



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