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ENANTIOSELECTION IN THE BIRCH REDUCTION-ALKYLATION OF A CHIRAL BENZOIC ACID DERIVATIVE

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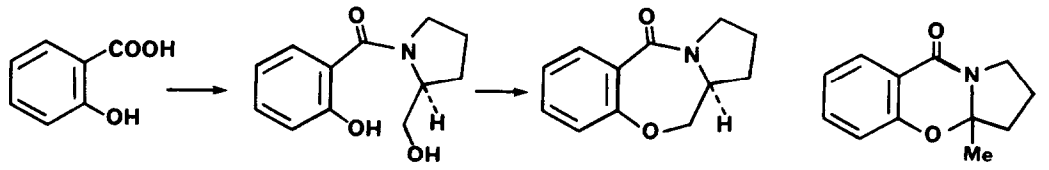
Summary: Preparation and diastereoselective Birch reduction-alkylation of benzoxazepenone 3 is described; conversion of 3 to ∿ enantiomerically pure 11 confirms the ~98:2 diastereoselection in the alkylation step.

The Birch reduction-alkylation of benzoic acid derivatives to give 6,6-disubstituted-1,4-cyclohexadienes is one of the most useful reactions in organic synthesis. Several applications to natural product synthesis have been recorded and we have developed a versatile method for preparation of 6-alkyl-6-carboalkoxy (and carboxamido)-2,4-cyclohexadien-1-ones by Birch reduction-alkylation of o-methoxybenzoic acid derivatives.[1] In this note, we report the first method for enantioselective Birch reduction-alkylation of a chiral benzoic acid derivative and illustrate an application of the method to the synthesis of tricyclo[4.3.1.$0^{3,7}$]decenone 11 in ∿ enantiomerically pure form.

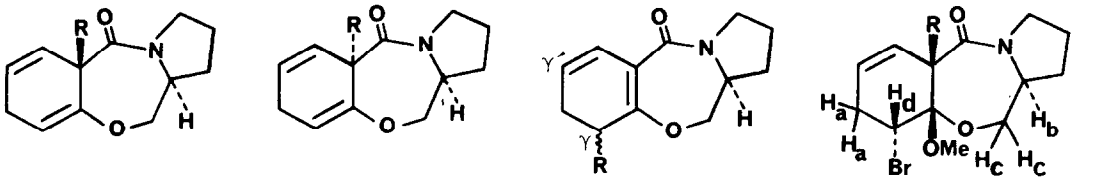
We have reported that the d-menthol ester of o-methoxybenzoic acid gave a 1:1 mixture of diastereoisomeric cyclohexadienes on Birch reduction-alkylation with methyl iodide.[1b] The absence of stereoselection must be due, at least in part, to the freedom of rotation of the chiral auxiliary about the ester C-O bond. We expected that restraining the chiral center to conformational movement within a benzo-fused seven-membered ring system might provide a measure of stereocontrol in the alkylation step.[2] Birch reduction-alkylation of N,N-dialkyl-2-methoxybenzamides had already been demonstrated;[1b] we, therefore, selected L-prolinol derived heterocycle 3 for exploratory studies.

Reaction of o-hydroxybenzoic acid (1) with N-methylmorpholine (2 equiv), N,N´-dicyclohexylcarbodiimide (1 equiv), 1-hydroxybenzotriazole (1 equiv), and L-prolinol[3] (1 equiv) in THF at 0° gave amide 2 in ∿ quantitative yield.[4] Cyclization of 2 was performed in ~80%

overall yield from 1 by use of the Mitsunobu reaction conditions.[5] Other methods of cyclization resulted in formation of varying amounts of benzoxazinone 4, presumably by elimination to the enamide (not shown) and intramolecular phenol-olefin addition.[6]



1 2 3 4



5a, R = Me
b, R = Et
c, R = $CH_2CH{=}CH_2$
d, R = $CH_2CH_2CH{=}CH_2$

6

7a, R = Me
b, R = H

8a, R = Me
b, R = $CH_2CH_2CH{=}CH_2$

Benzoxazepenone 3 underwent Birch-reduction with alkali metals in NH_3-THF solution in the presence of tert-butanol (1 equiv). The resulting amide enolate was subsequently treated with several common alkylation reagents; e.g., methyl iodide, ethyl iodide, allyl bromide and 4-bromo-1-butene (Table I). With methyl iodide, the product ratio (5a:6a) of 85:15, respectively, was found to be independent of the metal used in the reduction step (K, Na, Li; entries 1-3). With alkylation reagents more sterically hindered than methyl iodide, the diastereoselectivity of alkylation was outstanding (≥98:2; entries 4-6).

A small amount of γ-alkylation product 7a (~3%) was obtained from enolate alkylation with methyl iodide. This material appeared to be formed as a single diastereoisomer, but relative configuration has not as yet been determined. It is noteworthy that γ-alkylation occurred to give 7a (a tetrasubstituted vinylogous urethane) rather than γ′ to give a trisubstituted acrylamide (not shown). A small amount of the product of γ-protonation, 7b, was produced from alkylation with allyl bromide.

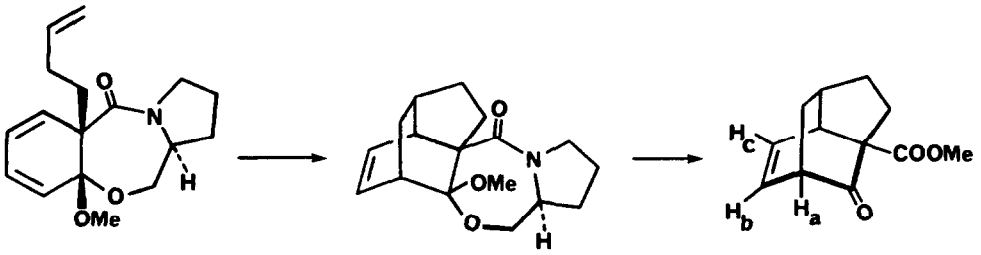
Table I. Stereoselective Birch Reduction-alkylations of 3.

entry	RX	metal	product ratio (5:6)[a]	isolated yield of 5, %[b]
1	MeI	K	85:15	67[c]
2	MeI	Na	85:15	-
3	MeI	Li	85:15	-
4	EtI	K	≥99:1	82
5	C_3H_5Br	K	≥98:2	75[d]
6	C_4H_7Br	K	~98:2	89

[a] Ratios determined by ^{1}H NMR integration and GC-mass spectrometric analysis.
[b] Isolated by flash chromatography on silica gel; diastereoisomeric purity ≥98%.
[c] 6a (mp 116-117°C, 8%) was obtained in chromatographic fractions eluting before 5a; 7a (~3%) was observed, but could not be obtained pure.
[d] 7b (~3%) was obtained in this experiment

The tentative assignment of relative configuration for the major diastereoisomer series 5a-d is based on NOE studies with derivative 8a (and corresponding derivatives of 6a), obtained by treatment of 5a with N-bromoacetamide (NBA) in methanol.[1] Significant enhancements (8-33%) of ^{1}H NMR resonances (200 MHz) were observed during irradiation at frequencies corresponding to the angular methyl group, the methoxy group, H_a, H_b, H_c, and H_d. Molecular models of 8a and all possible diastereoisomers indicate that only 8a can attain a conformation in which H_a, H_b, and H_c are in close proximity.

The diastereoselectivity of reductive alkylation of 3 with 4-bromo-1-butene was confirmed by conversion of 5d to the ∿ enantiomerically pure 3-carbomethoxytricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (11) by 1) treatment of 5d with NBA in methanol to give 8b, 2) dehydrobromination of 8b with 1,5-diazabicyclo[4.3.0]non-5-ene to give cyclohexadiene 9, and 3) intramolecular Diels-Alder addition of 9 to give 10 (refluxing toluene solution, mp 96°). Reaction of 10 with methanolic HCl at reflux temperature[3a,b] afforded 11 (oil) and returned the chiral auxiliary, L-prolinol. This substance, 11, when compared to racemic 11 prepared from methyl o-methoxybenzoate[8] was shown to be ≥98% enantiomerically pure by chiral shift reagent ^{1}H NMR analysis with Eu(hfc)$_3$.[9] Specifically, resonances due to the methoxy group, H_a, H_b, and H_c were resolved when Eu(hfc)$_3$ was added to racemic 11 (one molar equiv). With 11 prepared from 5d, only one set of signals was observed; as a result of NMR experiments with 8b, the absolute configuration of 11 has been tentatively assigned as shown.



9 10 11

Continuing studies are directed at 1) the utilization of this chiral auxiliary method in enantioselective natural product syntheses, 2) an examination of the diastereoselectivity of aldol condensations of the chiral amide enolate derived from 3 and related enolates, and 3) the development of protocols for the conversion of benzoic acids to a wide range of optically active cyclohexanes for use in organic synthesis.[10]

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References and Notes

1. (a) Schultz, A. G.; Dittami, J. P. Tetrahedron Lett. 1983, 24, 1369. (b) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. J. Org. Chem., in press and references cited therein.
2. For a report of stereoselection in the alkylation of cyclic bis-lactim ethers derived from L-amino acids, see Schöllkopf, W.; Groth, U.; Westphalen, K. O.; Deng, C. Synthesis 1981, 969.
3. For the use of prolinol derivatives as chiral auxiliaries see (a) Sonnet, P. E.; Heath, R. R. J. Org. Chem. 1980, 45, 3137. (b) Evans, D. A.; Takacs, J. M. Tetrahedron Lett. 1980, 21, 4233. (c) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. Helv. Chim. Acta 1977, 60, 301. (d) Enders, D.; Eichenauer, H. Angew. Chem. Int. Ed. Engl. 1979, 18, 397. (f) Kolb, M.; Barth, J. Angew. Chem. Int. Ed. Engl. 1980, 19, 725. (g) Mukaiyama, T. Tetrahedron 1981, 37, 4111.
4. Compounds 2, 3, 4, 5c, 5d, 6a, 8a, 8b, 11 gave satisfactory combustion analyses.
5. Mitsunobu, O. Synthesis 1981, 1 and references cited therein.
6. Benzoxazinone 4 (oil) was obtained in 73% yield from the chloromethyl derivative of 2 (mp 136-138°C, from treatment of 2 with $SOCl_2$-triethylamine in $CHCl_3$; 74% yield) by reaction with K_2CO_3 in acetone.
7. Birch reduction-alkylation reaction conditions were similar to those described in detail in reference 1.
8. Schultz, A. G.; Snead, T.; Lavieri, F. P. manuscript in preparation.
9. Available from Aldrich Chemical Company.
10. An analysis of stereochemical control in reactions of amide enolates derived from 3 together with complete experimental details will be presented in the full paper resulting from this work.

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