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THE ENANTIOSELECTIVE CONVERSION OF ORTHO-SUBSTITUTED BENZOIC ACIDS TO CHIRAL CYCLOHEXANE DERIVATIVES

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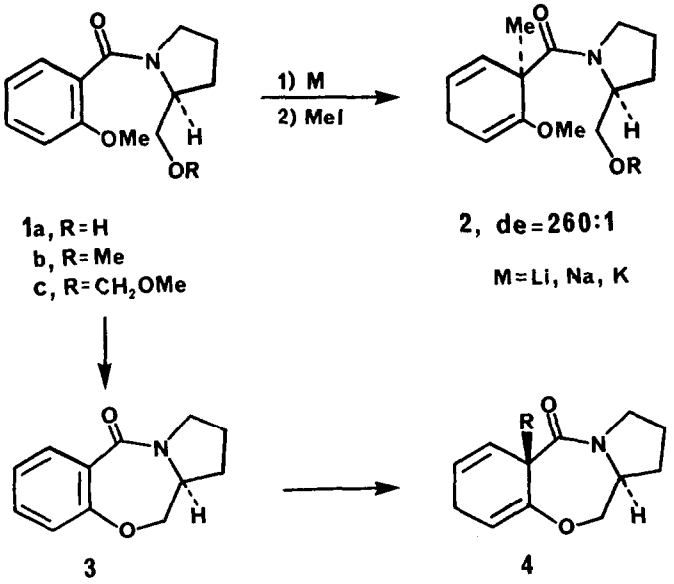
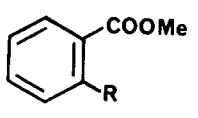
Summary: The diastereoselectivity of reductive methylation of 1a-1c to give 2a-2c and 11 to give 12 is 260:1 and >99:1, respectively.

Acylation of L-prolinol with o-anisoyl chloride provides amide 1a, which, when treated with sodium hydride in DMF (120°C, 18 h), gives crystalline benzoxazepenone 3.[1] The Birch reductive alkylation of 3 has been reported to give 4 with good to excellent diastereoselectivity.[2] We now report Birch reductive alkylations of 1a-1c. These reactions occur with remarkably high diastereoselectivity to give 2 with configuration at the new chiral center opposite to that obtained with 3.[3]

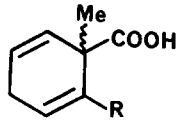


Birch reduction of the series 1a-1c, in NH_3-THF solution in the presence of tert-butyl alcohol (1 equiv), followed by alkylation of the resulting amide enolate with methyl iodide gives 2 and the corresponding diastereoisomer (de = 260:1) in 82-85% isolated yields.[4] The ratio of diastereoisomers is independent of the substituent attached to the prolinol oxygen atom and the alkali metal (Li, Na, K) used in the reduction step.

The diastereoisomeric composition of 2 was determined by comparison to the mixture of products obtained by 1) Birch reduction-methylation of 5a, followed by ester saponification to give racemic 6a, and 2) coupling of 6a with L-prolinol, followed by methylation of the resulting amido alcohols (NaH, THF, MeI) to give 7a. The diastereoisomeric nature (~50:50) of 7a so prepared was apparent by observation of ^1H NMR spectra (200 MHz), GC-MS,[5] and flame ionization VPC analysis.[6]



5a, R=OMe
b, R=Me



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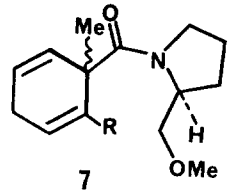

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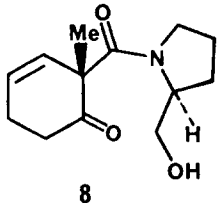
Stereochemical configuration of 2 was deduced by chemical interconversions. Acid-catalyzed hydrolysis of 4 (R = Me) gave cyclohexenone 8 (oil), while the corresponding minor diastereoisomer (not shown) was converted to 9 (mp 98-9°C). Hydrolysis of 2c gave 9 (mp 98-9°C) rather than 8, thus establishing the stereoselectivity of the reductive alkylation of the series 1a-1c.



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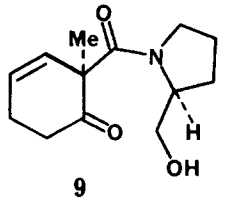

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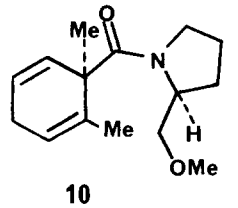

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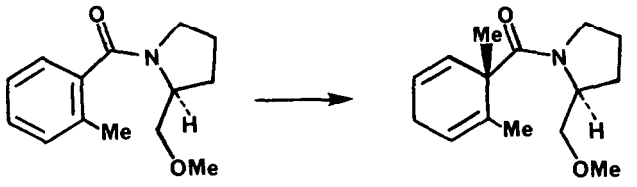
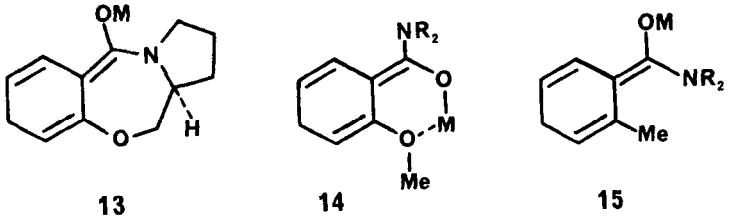
The inversion of the sense of asymmetric induction in alkylations of amide enolates derived from 1a-1c, relative to that observed with 3, appears to be a result of chelation control.[7] A priori, two sites of chelation are available to the alkali metal associated with the amide enolate: the methoxy group on the aromatic ring and/or the prolinol oxygen atom. The o-toluoyl derivative, 11, was prepared to test the importance of the ring methoxy group. Reductive methylation of 11 gives 12 as the major diastereoisomer (de>99:1) in 90%

isolated yield. Following the analytical procedures developed for examination of 2, 5b was converted to the diastereoisomeric mixture 7b, and 2b was converted to 10 by 1) acid-catalyzed enol ether hydrolysis, 2) methyl Grignard addition to the resulting ketone carbonyl group, and 3) acid-catalyzed dehydration of the derived tertiary alcohol (~70% overall yield). ^{1}H NMR and GC-MS data, along with quantitative VPC analysis,[8] demonstrate that 10 corresponds to the minor diastereoisomer obtained from the reductive methylation of 11.



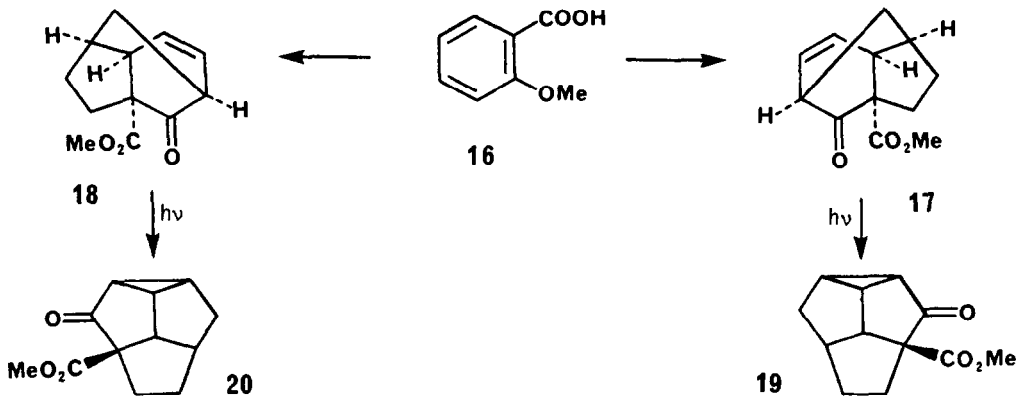
11 **12, de >99:1**

Clearly, the ring methoxy group in 1a-1c[9] exerts a powerful stereodirecting effect, suggesting that enolates derived from these benzamides may have geometry as shown in 14. Alkylations of enolates 14 occur with α-selectivity. On the other hand, 13 and the enolate derived from 11 both undergo alkylation with β-selectivity. These data suggest that the enolate generated by Birch reduction of 11 may have the same configuration as 13; e. g., 15. A more detailed mechanistic analysis must await additional experimentation.



13 **14** **15**

Thus, chiral cyclohexenones (e. g., 8 and 9), as well as chiral 1,4-cyclohexadienes (e. g., 10 and 12) are available in both enantiomeric forms from the readily available chiral auxiliary L-prolinol and simple ortho-substituted benzoic acids. A demonstration of the synthetic potential of the method is provided by the conversion of o-methoxybenzoic acid 16 to tricycle 17 and enantiomer 18, from 3 and 1c, respectively, via an intramolecular Diels-Alder strategy.[2a] Chiral shift reagent ^{1}H NMR along with ORD spectroscopic studies with 17 and 18 substantiate that these materials are enantiomeric and that they have been prepared with ee >98%. The photochemical conversion of the racemate 17 + 18 to 19 + 20 already has been reported in detail.[10] These and related strategies based on the chemistry of 1 are expected to provide access to an unusually diverse array of natural product targets.



Acknowledgment. This work was supported by the National Institutes of Health (GM 26568 and GM 33061).

References and Notes

1. This procedure for preparation of 3 is superior to that reported in reference 2. It should be suitable for large-scale production of 3.

2. (a) Schultz, A. G.; Sundararaman, P. Tetrahedron Lett. 1984, 25, 4591. (b) Schultz, A. G.; Puig, S. J. Org. Chem. 1985, 50, 915.

3. Stereochemical configuration in the series 4 has been determined by ^{1}H NMR and NOE studies, by single crystal X-ray diffraction studies with a derivative of 4 (R = Me), and by total synthesis of (-)-longifolene (see reference 2b).

4. Yields are reported for analytically pure material isolated by flash chromatography on silica gel.

5. Chemical ionization spectra were obtained on a Hewlett-Packard 5087A GC-MS system (methane, chemical ionization gas).

6. VPC analyses were performed on a Hewlett-Packard HP 5710A gas chromatograph equipped with a 16 ft x 1/8 in. stainless steel column filled with 5% QF-1 on Chromosorb W, 80-100 mesh size; column temperature 150°C for two min, temperature programmed to 250°C at 2°C per min (2b, 33.7 min; second diastereoisomer, 34.7 min). Peak areas were measured with a Hewlett-Packard HP 3380A integrator.

7. "Asymmetric Synthesis - A Multivolume Treatise"; Morrison, J. D., Ed., Academic Press: New York, 1984.

8. Column temperature 140°C for two min, temperature programmed to 220°C at 2°C per min (12, 28.2 min; second diastereoisomer, 10, 29.8 min).

9. It is noteworthy that no change in diastereoselectivity was noted for reductive alkylations of the series 1a-1c. In contrast, the sense of asymmetric induction in alkylation of amide enolates derived from prolinol and propionic acid is strongly influenced by the nature of the substituent on the alcohol oxygen atom (H vs. Me); see a) Evans, D. A.; Takacs, J. M. Tetrahedron Lett. 1980, 21, 4233. b) Sonnett, P. E.; Heath, R. R. J. Org. Chem. 1980, 45, 3139.

10. Schultz, A. G.; Lavieri, F. P.; Snead, T. E. J. Org. Chem., in press.

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