An Asymmetric Intramolecular Alkylation to form a Bicyclo[3.1.0]hexanone Derivative

David P. G. Hamon* and Neil J. Shirley

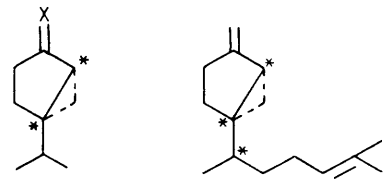
Department of Organic Chemistry, University of Adelaide, Adelaide, South Australia 5001, Australia

The epoxy ketol (−)-2-hydroxymethyl-1-oxaspiro[2.5]octan-6-one (**7b**) isomerises with base to 1-(1,2-dihydroxy-1-methylethyl)bicyclo[3.1.0]hexan-4-one (**5b**) with high diastereoselectivity.

A recent report[1] has described the asymmetric synthesis of sabina ketone (**1**) *via* a Simmons–Smith reaction on a homochiral acetal derivative. In principle, this route also gives access to natural products of the thujane group, *e.g.* sabinene (**2**). In this paper we describe an alternative approach to the asymmetric synthesis of the bicyclo[3.1.0]hexanone skeleton which involves an intramolecular alkylation reaction. This reaction controls the stereochemistry at three chiral centres and this approach should allow the synthesis of members of the thujane group, and also the related group of sesquiterpenes, *e.g.* sesquisabinene (**3**), with control of the stereochemistry at the chiral centres designated by asterisks.

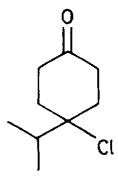
There have been two reports[2,3] of the synthesis of racemic sabina ketone by means of intramolecular alkylation reactions. In order to extend this approach to the asymmetric synthesis of this family of natural products, an asymmetric deprotonation of the precursor ketone is required. There has been a report[4] of the intermolecular asymmetric deprotonation of cyclohexanone derivatives but application of this procedure to the chloro ketone (**4**) gave sabina ketone with no measurable asymmetric induction.[5] We considered that an intramolecular regioselective deprotonation might give better control of the stereochemistry in the intramolecular alkylation reaction and we designed the molecules (**7**) to establish this contention. We report here the syntheses of epoxides (**7**) and show that epoxide (**7b**) rearranges with base to give a mixture of the bicyclo[3.1.0]hexanone diastereoisomers (**5**) which contains 87% of one isomer believed to have the absolute configuration (**6**).

The allylic alcohols (**11a**) and (**11b**) were prepared by the route outlined in Scheme 1. Reaction of the allylic alcohol (**11a**) with *m*-chloroperbenzoic acid gave racemic ketol epoxide (**7a**) and this was converted into the methoxymethyl ether derivative (**7c**). Treatment of this derivative with sodium ethoxide in ethanol† gave an approximately 1 : 1 mixture of

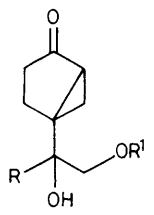


(**1**) X = O
(**2**) X = CH_2

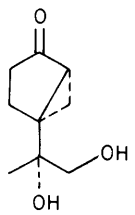
(**3**)



(**4**)

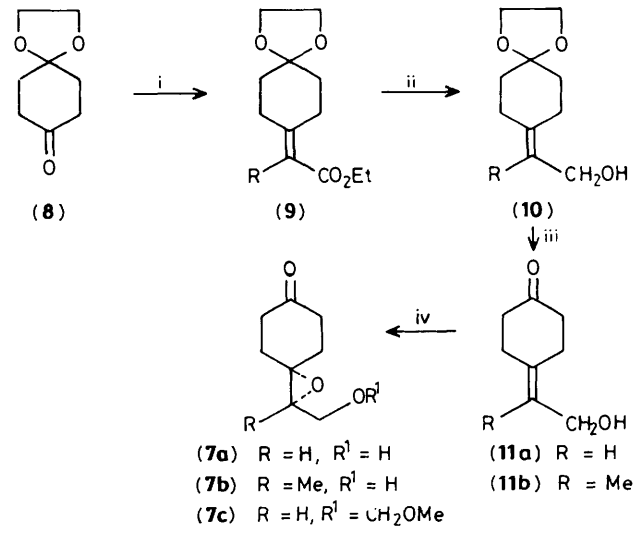


(**5a**) R = H, R^1 = H
(**5b**) R = Me, R^1 = H
(**5c**) R = H, R^1 = CH_2OMe



(**6**)

† It is assumed EtOH would swamp any intramolecular effect.



Scheme 1. *Reagents and conditions*: i, either $(EtO)_2POCH_2CO_2Et$, NaH, tetrahydrofuran (THF) or $(EtO)_2POCHMeCO_2Et$, NaH, THF, reflux; ii, $LiAlH_4$, ether, reflux; iii, $(CO_2H)_2$, H_2O, Me_2CO; iv, either *m*-$ClPhCO_3H$, CH_2Cl_2 or $Ti(OPr^i)_4$, CH_2Cl_2, (+)-DET, Bu^tOOH, −23 °C.

the diastereoisomers (**5c**) as shown by the 300 MHz ^1H n.m.r. spectrum. In particular, the cyclopropyl protons resonated as two sets of peaks. One set was observed at δ 1.0(5) dd, 1.5 dd, and 1.9 dd (superimposed on other peaks). The other set was at δ 1.1(5) dd, 1.3(5) dd, and 1.8 dd. These relationships were established by a 2D homonuclear shift-correlated spectrum (COSY). Likewise a mixture of diastereoisomers (**5b**), obtained from the racemic epoxide (**7b**) by treatment with base in 1,2-dimethoxyethane (DME), showed distinct resonances at δ 0.9(7) dd, 1.5 (6) dd, 1.9(3) m superimposed (cyclopropyl), 1.2(1) s (CH_3), and 3.5(5), 3.7(5) ABq ($-CH_2-O$) for one diastereoisomer. The other diastereoisomer gave resonances at δ 1.0(7) dd, 1.68 m, 1.87 m superimposed (cyclopropyl), 1.28 s (CH_3), and 3.5(2), 3.6(2) ABq ($-CH_2-O$). These relationships were confirmed by a COSY experiment.

Sharpless epoxidation[6] of the allylic alcohol (**11b**), with (+)-diethyl tartrate (DET) as the chiral inductor, gave the optically active epoxide (**7b**) as an oil, $[\alpha]_D$ −2.56° (*c* 2.54, $CHCl_3$) determined to be of ≥90% enantiomeric excess (e.e.) from the 300 MHz ^1H n.m.r. spectrum of its (*S*)-MTPA[7] ester. Treatment of this optically active epoxide in DME (6×10^{-3} M) at reflux with an equimolar amount of potassium t-butoxide for 15 min gave a mixture of the diastereoisomers (**5b**) in poor chemical yield (14%) but with high diastereoselectivity (92 : 8) as shown by 300 MHz ^1H n.m.r. spectroscopy.

It has been shown that the direction of asymmetric epoxidation can be predicted.[8] Since (+)-DET was used as the chiral inductor, the absolute configuration of the epoxide (**7b**) is almost certainly as shown. It seems likely, therefore, that the absolute configuration of the major diastereoisomer (87% of the mixture, diastereoselectivity 92 : 8, enantioselectivity 95 : 5) is as shown in (**6**). The diastereoselection probably comes about either by direct intramolecular deprotonation by the alkoxide of alcohol (**7b**), or by solvation of the base by the hydroxy group which thereby directs the regiochemistry of deprotonation. It should be noted that this reaction controls the stereochemistry at three chiral centres.

It is hoped that conditions can be found to improve the chemical yield of the cyclisation whilst still maintaining the diastereoselectivity, and that these conditions will also lead to diastereoselectivity when applied to the cyclisation reactions of the epoxides (**7a**) and (**7c**). In these latter cases the third chiral centre under control will be a secondary alcohol. Such a group should be useful for the construction of the side chain, necessary for the synthesis of the sesquiterpenes [*e.g.* (**3**)], with control of the stereochemistry at that centre.

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References

1 E. A. Mash and K. A. Nelson, *Tetrahedron*, 1987, **43**, 679.
2 Y. Gaoni, *Tetrahedron*, 1972, **28**, 5525.
3 D. P. G. Hamon and N. J. Shirley, *Aust. J. Chem.*, 1987, **40**, 1321.
4 N. Simpkins, *J. Chem. Soc., Chem. Commun.*, 1986, 88.
5 N. J. Shirley, Ph.D. Thesis, University of Adelaide, submitted 1987.
6 B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 464.
7 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
8 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974.