5,6-Dehydrocamphor: a Chiral Intermediate in Terpenoid Synthesis

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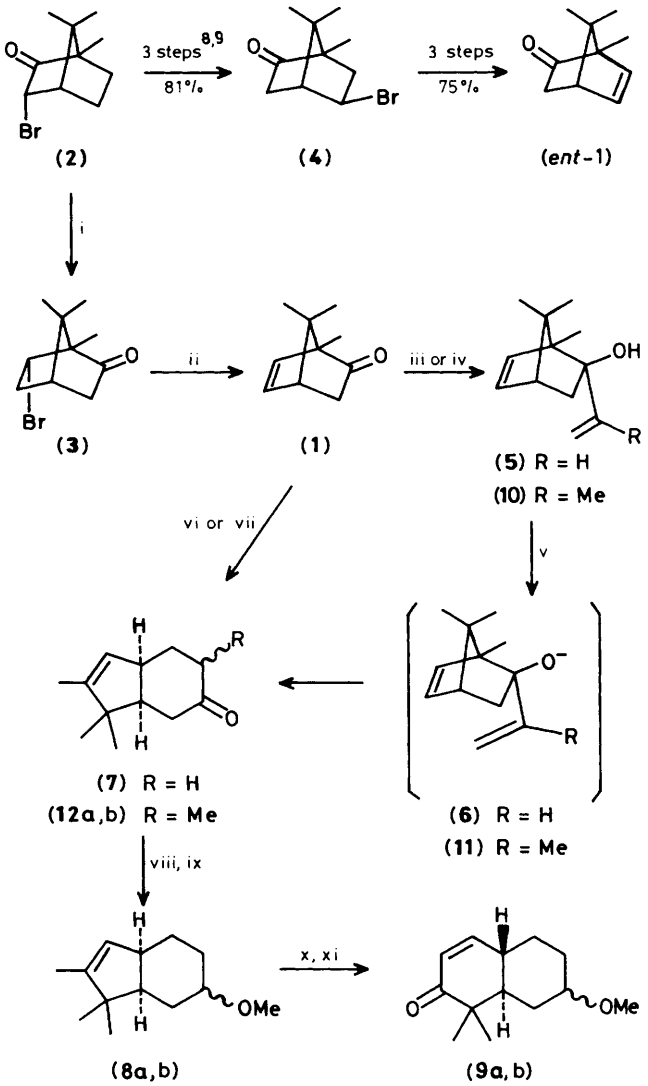
Anionic oxy-Cope rearrangements of alkoxides derived from 5,6-dehydrocamphor provide chiral products which have potential as intermediates in the enantiospecific synthesis of terpenoids.

The anionic oxy-Cope rearrangement[1] is an important reaction in synthetic methodology. Alkoxides derived from norbornenone derivatives[2] readily undergo this arrangement to provide polycyclic compounds which can serve as intermediates in natural product synthesis. We considered the possibility that anionic oxy-Cope rearrangement of alkoxides, derived from (+)-5,6-dehydrocamphor (**1**) or its enantiomer (***ent*-1**), could provide bicyclic compounds which could serve as chiral intermediates in the enantiospecific synthesis of a wide variety of terpenoids.

Literature routes[3—5] to 5,6-dehydrocamphor (**1**) involve 7—9 steps and depend on remote oxidation of (+)-bornyl acetate at the C(5) position.[6] The inconvenience of these multi-step routes prompted us to develop alternative procedures (Scheme 1) which involve simple transformations of commercially available (+)-*endo*-3-bromocamphor (**2**) to



Scheme 1. *Reagents and conditions:* i, $ClSO_3H$, 15 min, 50 °C (*ca.* 50%); ii, KOH, Me_2SO/H_2O (7:1), 24 h, 100 °C (*ca.* 50%); iii, CH_2=CHMgBr, THF (92%); iv, CH_2=C(Me)MgBr, THF (90%); v, KH, THF, 20 °C (85%); vi, CH_2=C(Me)MgBr, THF; reflux, 1.5 h (89%); vii, CH_2=CHMgBr, THF; reflux, 24 h (*ca.* 95%); viii, L-selectride, THF, 0 °C (90%); ix, KH, THF, MeI (98%); x, O_3, CH_2Cl_2, MeOH, −78 °C Ph_3P; xi *p*-$MeC_6H_4SO_3H$, C_6H_6, reflux (x, xi; 87%).

(−)-*endo*-6-bromocamphor (**3**)† or (+)-*exo*-5-bromocamphor (**4**)[8,9] and hence to (+)-5,6-dehydrocamphor (**1**), $[\alpha]_D$ + 753° (*c* 2.1, EtOH) and its enantiomer (***ent*-1**), $[\alpha]_D$ − 718° (*c* 2.1, EtOH) [lit.,[3] − 735° (*c* 1.0, EtOH), lit.,[4] − 699° (*c* 5.0, EtOH)], respectively.

In subsequent investigations we discovered that, in contrast with camphor,[10] addition of vinylmagnesium bromide to (+)-5,6-dehydrocamphor (**1**) occurred in excellent yield (*ca.* 90%) to provide 2-vinyl-5,6-dehydroisoborneol (**5**). Treatment of (**5**) with KH/tetrahydrofuran (THF) at room temperature for 15 min led to the formation of *cis*-ketoalkene (**7**), $[\alpha]_D$ − 119° (*c* 0.55, $CHCl_3$), which was subsequently converted (Scheme 1) to bicyclic enone (**9a,b**; α-OMe: β-OMe ~ 6:1)[11] in *ca.* 60% overall yield. When (+)-5,6-dehydrocamphor (**1**) was treated with 2-propenylmagnesium bromide at room temperature for 30 min followed by refluxing in THF for two hours, anionic oxy-Cope rearrangement occurred *in situ* and a mixture of diastereomeric bicyclic ketones (**12a,b**) was obtained directly in *ca.* 90% yield. Later investigations revealed that *in situ* formation of *cis*-ketoalkene (**7**) can also be accomplished in *ca.* 95% yield.

Future investigations will be concerned with the stereoselective introduction of an angular methyl group at the C(10) position in suitable derivatives of (**9**) and with the use of other alkenyl Grignard reagents (chiral and achiral) to generate more complex bicyclic compounds which can serve as intermediates in the synthesis of diterpenoids, sesterterpenoids and triterpenoids.[13]

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† We have investigated the mechanism of rearrangement of (+)-*endo*-3-bromocamphor (**2**) to (−)-*endo*-6-bromocamphor (**3**) (Scheme 1) using 10-deuterio-*endo*-3-bromocamphor as substrate and the results of these studies[7a] have been outlined in previous publications.[7b,c]

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11 The *trans* stereochemistry shown for methoxy-enone (**9a,b**) has not been established directly and is based on *X*-ray crystallographic analysis (S. Rettig and J. Trotter, unpublished results) of a dimer produced from the corresponding acetoxy-enone, *cf.* D. L. Kuo, Ph.D. Thesis, U.B.C., Vancouver, Canada, 1987.

12 A preliminary account of this work was presented by one of us (D. L. K.) at the 70th C.I.C. Conference, Quebec City, June, 1987.