Tetrahedron Letters, Vol.32, No 39, pp 5219-5222, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

USE OF THE Me_3Sn FUNCTION AS A READILY REMOVABLE 'ANCHORING' GROUP IN THE SYNTHESIS OF ENANTIOMERICALLY PURE BICYCLIC ALCOHOLS AND KETONES

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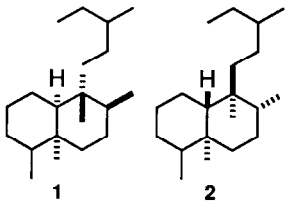
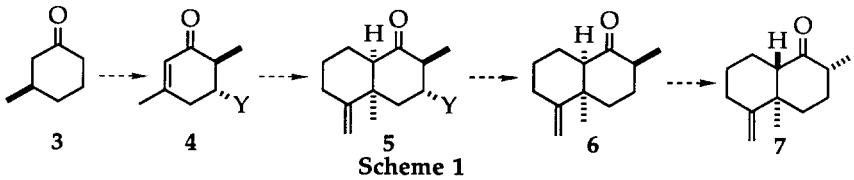
*Summary: Subjection of (5R, 6R)-(-)-3,6-dimethyl-5-trimethylstannyl-2-cyclohexen-1-one (**11**) to appropriate annulation sequences provides the cis-fused ketones **15**, **20**, and **21**, which, upon reduction (Li, NH_3, THF,t-BuOH) are converted smoothly into the enantiomerically pure bicyclic alcohols **16**, **22**, and **23**, respectively. Compound **16** is readily transformed into the unichiral ketones **6** and **7**.*

Annulation sequences that serve to convert monocyclic substrates into functionalized bicyclic intermediates often play key roles in specific natural product syntheses. A current research program in our laboratory involves the development of a general synthetic route to *enantiomerically pure*, physiologically active natural products belonging to the *cis*- and *trans*-clerodane families of diterpenoids, which possess the general carbon skeleta shown in **1** and **2**, respectively. In accordance with our synthetic plan, an initial goal of this program was to achieve efficient syntheses of the optically active ketones **6** and **7**. It appeared at the outset that the readily available



1 **2**



3 **4** **5** **6** **7**

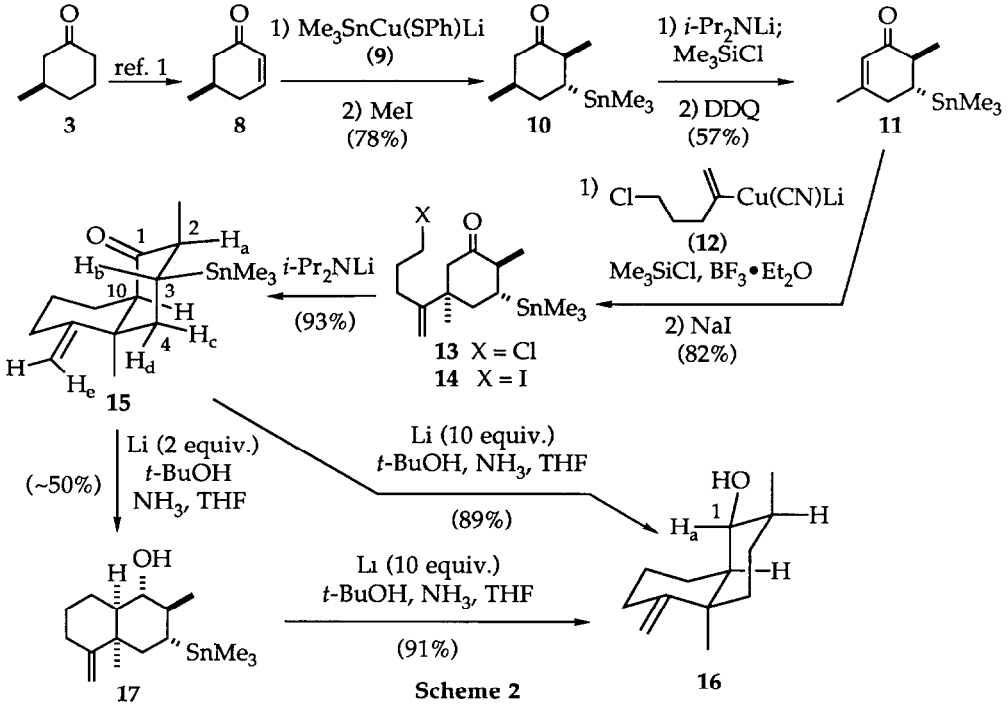
Scheme 1

ketone (*R*)-(+)-3-methylcyclohexanone (**3**) would serve as a convenient starting material for this endeavor and that the reaction sequence outlined in general terms in **Scheme 1** would provide a concise route to the required ketones. In this synthetic pathway, it was envisaged that enantiomeric integrity would be preserved by placing a group Y at C_5 of compound **3** prior to introduction of the necessary C_2-C_3 double bound (see **3** →**4**). Ideally, the nature of Y should be such that, after completion of the required annulation sequence (**4** →**5**), this group could be removed efficiently in a single synthetic step. We report herein that the trimethylstannyl function serves admirably in this regard and, notably, that this moiety can be removed from organic substrates by means of a dissolving metal reduction.

The dextrorotatory enone **8** is readily derived from the ketone **3**[1] (see **Scheme 2**). Treatment (THF, -20°C) of **8** with lithium (phenylthio)(trimethylstannyl)cuprate (**9**),[2] followed by addition of iodomethane in hexamethylphosphoramide (HMPA), provided a single product

10,[3,4] $[\alpha]_D^{28}$ +134° (c 1.02, MeOH). Conversion of **10** into the enone **11** {$[\alpha]_D^{29}$-45° (c 1.072, MeOH)} was accomplished by oxidation (2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), collidine, PhH)[5] of the corresponding enol trimethilsilyl ether.

Reaction (THF, -78°C) of the enone **11** with the lower order cuprate reagent **12**[6] in the presence of Me_3SiCl *and* $BF_3 \bullet Et_2O$[9] afforded a single product **13**.[10] Conversion (NaI, acetone) of **13** into the iodide **14**, followed by intramolecular alkylation (LDA, THF, -78°C→30°C) of the latter substance, produced the *cis*-fused bicyclic ketone **15**, $[\alpha]_D^{28}$ +109° (c 1.014, MeOH), m.p 55.5-56°C. It is pertinent to note explicitly that, in the overall conversion of **3** into **15**, the Me_3Sn group served two important functions. First, it preserved enantiomeric integrity in the intermediate **11** and, second, its stereochemical orientation ensured that, even under equilibrating conditions, the two epimerizable chiral centers in **15** (C-2 and C-10) would possess, at least predominantly, the configurations indicated in **15**. Indeed, **15** consisted of a single

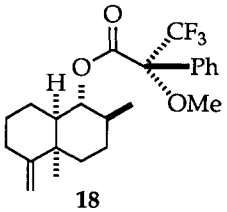


Scheme 2

isomer and appropriate ^1H NMR experiments confirmed the configurational assignments. The fact that the signal due to H_b (δ 1.81) displays two strong couplings ($J_{ab} \approx J_{bc} \approx 14$ Hz) and one weak coupling (J_{bd} = 2.5 Hz) showed that the protons H_a and H_b are both axially oriented. Furthermore, the *cis* ring fusion was established by use of a nuclear Overhauser enhancement difference (NOED) experiment in which irradiation at δ 1.81 (H_b) caused an increase in the intensity of the signal due to the olefinic proton H_e (δ 4.58).

It was gratifying to find that the trimethylstannyl function in **15** could be removed smoothly and efficiently by use of an alkali metal reduction. Thus, treatment (-78°C, 1h; reflux, 1h) of **15** with an excess of lithium in THF-NH_3 in the presence of *tert*-butyl alcohol provided (89%) the olefinic alcohol **16**, $[\alpha]_D^{24}$ +37° (c 0.892, $CHCl_3$), m.p. 87.5-88°C. On the other hand , reduction of **15** with 2 equivalents of lithium provided the alcohol stannane **17** (~50%) in addition to some starting material **15** and the alcohol **16**. Further reduction of **17** with excess lithium gave **16** very efficiently. Thus, reduction of the carbonyl group in **15** is marginally faster than reductive removal of the Me_3Sn function.

The (expected) configuration of C-1 in **16** was confirmed by the fact that, in the ^1H NMR spectrum of this substance, the signal due to H_a appeared (after addition of D_2O) as a triplet with J = 10 Hz. In order to establish the enantiomeric purity of **16**, this material was subjected to separate reactions with (+)- and (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride.[11] The ^1H and ^{19}F NMR spectra of the two products (**18** and **19**, respectively) displayed no diagnostic signals due to the corresponding diastereomers (*i.e.*, the enantiomers of **19** and **18**, respectively).



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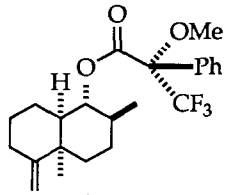

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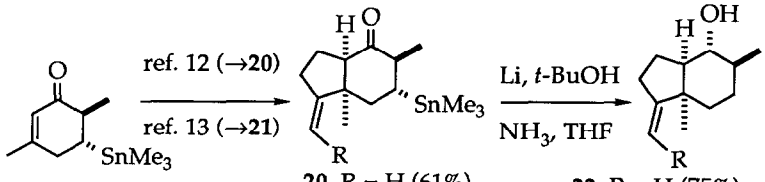
In order to demonstrate further the generality and usefulness of the reductive removal of the Me_3Sn moiety from carbocycles, the enone **11** was subjected to methylenecyclopentane[12] and (Z)-ethylidenecyclopentane[13] annulation sequences to provide cleanly the functionalized ketones **20** {$[\alpha]_D^{26}$+77° (c 1.14, MeOH); m.p. 60°C} and **21** {$[\alpha]_D^{26}$+77° (c 0.978, MeOH); m.p. 56-57°C}, respectively. Reduction of the latter substances under conditions identical with those described above (**15**→**16**) produced the *cis*-fused bicyclic alcohols **22** {$[\alpha]_D^{23}$-72° (c 0.716, $CHCl_3$); m.p. 68.5-69°C} and **23** {$[\alpha]_D^{25}$-35° (c 0.995, $CHCl_3$); m.p. 52.5-53.5°C}. The stereochemical assignments for compounds **20-23** were fully corroborated by ^1H NMR spectroscopy (coupling constants; NOED experiments).



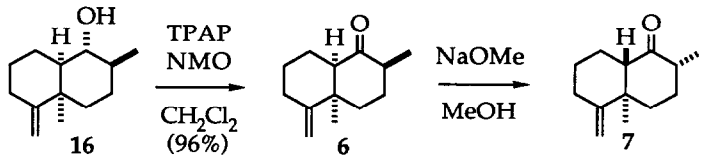
11

20 R = H (61%)
21 R = Me (54%)

22 R = H (75%)
23 R = Me (66%)

The work summarized above showed that the readily available ketone (**R**)-(+)-3-methylcyclohexanone (**3**) can serve as a suitable starting material for the preparation of functionalized, enantiomerically pure bicyclic intermediates. The potential use of this new methodology for the synthesis of substances suitable for elaboration into natural products is obvious. For example, oxidation of the alcohol **16** with tetrapropylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMO) and 4Å molecular sieves[14] gave the *cis*-fused bicyclic ketone **6** {$[\alpha]_D^{25}$-33° (c 1.175, $CHCl_3$)}. Treatment of **6** with sodium methoxide in methanol provided the *trans*-fused ketone **7** {$[\alpha]_D^{25}$+144° (c 1.38, $CHCl_3$)}. The use

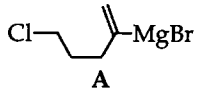
of compounds **6** and **7**[15] for the synthesis of enantiomerically pure *cis*- and *trans*-clerodane diterpenoids (see **1** and **2**) is currently under investigation.



Acknowledgements: We thank FCAR(Québec) and UBC for postgraduate scholarships to J.Y.R. and NSERC(Canada) and Merck Frosst Canada Inc. for financial support.

References and notes:

1. Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta*, **1978**, *61*, 2755.
2. Piers, E.; Morton, H.E.; Chong, J.M. *Can. J. Chem.* **1987**, *65*, 78.
3. All compounds reported herein exhibited spectra in accord with structural assignments and gave satisfactory C and H analyses.
4. Treatment of **10** with NaOMe in MeOH gave a mixture of **10** and its C-2 epimer, in a ratio of ~ 1:1.
5. Fleming, I.; Paterson, I. *Synthesis*, **1979**, 736.
6. Reagent **12** was prepared by treatment of a THF solution of 5-chloro-2-lithio-1-pentene[7] with the soluble copper(I) salt CuCN•2LiCl.[8]
7. Piers, E.; Yeung, B.W.A.; Rettig, S.J. *Tetrahedron*, **1987**, *43*, 5521.
8. *Cf.* Knochel,P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
9. Interestingly, reaction of **11** with **12** in the presence of Me_3SiCl alone was very slow and provided the desired product **13** in only 30-50% yield, while a similar reaction in the presence of $BF_3•Et_2O$ alone gave **13** in 64% yield. However, use of both additives resulted in a facile, efficient (86%) transformation. *Cf.* Wu, T.-C.; Xiong, H.; Rieke, R.D. *J. Org. Chem.* **1990**, *55*, 5045.
10. Reaction (THF, -78°C) of **11** with the Grignard reagent **A** in the presence of $CuBr•Me_2S$ and $BF_3•Et_2O$[7] was less stereoselective and afforded (90%) a mixture of **13** and the corresponding C-5 epimer in a ratio of about 4:1.



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11. Dale, J.A.; Dull, D.L.; Mosher H.S. *J. Org. Chem.* **1969**, *34*, 2543.
12. Piers, E.; Karunaratne, V. *Tetrahedron*, **1989**, *45*, 1089.
13. Piers, E.; Gavai, A.V. *J. Org. Chem.* **1990**, *55*, 2380.
14. Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. See also *Aldrichim. Acta*, **1989**, *22*, 53.
15. Racemic **7** has been employed as an intermediate for the total synthesis of (±)-palauolide, (±)-isolinaridiol and (±)-isolinaridiol diacetate: Piers, E.; Wai, J.S.M. *J. Chem. Soc., Chem. Commun.* **1987**, 1343; **1988**, 1245.

(Received in USA 21 June 1991)