BIFUNCTIONAL REAGENTS IN ORGANIC SYNTHESIS: STEREO-CONTROLLED METHODS FOR THE SYNTHESES OF FUNCTIONALIZED *trans*-FUSED BICYCLO[3.3.0]OCTANE AND BICYCLO[4.3.0]NONANE SYSTEMS

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*Abstract: Conjugate additions of the bifunctional organocopper(I) reagents 2-(trimethyl-stannyl)allylcopper(I)-dimethyl sulfide (1) and lithium (3-trimethylgermylbut-3-en-1-yl)(cyano)-cuprate (2) to the cyclopent-1-enecarbaldehyde substrate 9 play key roles in the development of new methods for the stereoselective synthesis of functionalized* trans-*fused bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems, respectively.* Copyright © 1996 Elsevier Science Ltd

The search for efficient methods for the configurationally controlled construction of *trans*-fused bicyclic compounds is of continuing interest to practitioners of organic synthesis.[1,2] Recent reports from this laboratory have described, *inter alia*, the preparation of the novel bifunctional organocopper(I) reagents 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (1)[3] and lithium (3-trimethylgermylbut-3-en-1-yl)(cyano)cuprate (2).[4] Furthermore, it was shown[3,4] that, under appropriate reaction conditions, these reagents efficiently transfer, in a conjugate sense, the 2-(trimethylstannyl)allyl and 3-trimethylgermylbut-3-en-1-yl groups to α,β-unsaturated ketones 3 to afford products of general structures 4 and 5, respectively. We report herein that reagents 1 and 2 can be employed effectively for the stereocontrolled synthesis of *trans*-fused bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems, respectively.
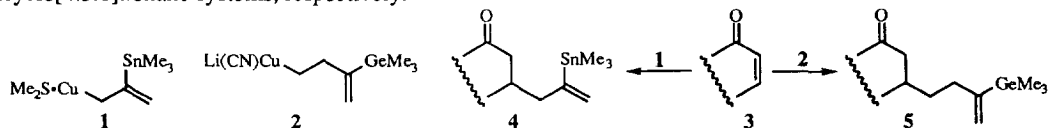
Conversion[5] of the keto ketal 6[6] (Scheme 1) into the alkenyl triflate 7,[7] followed by Pd(0)-catalyzed methoxycarbonylation[8] of the latter substance, provided the α,β-unsaturated ester 8, which was readily transformed into the corresponding aldehyde 9 via a straightforward reduction-oxidation sequence. Bromotrimethylsilane-promoted conjugate addition of the organocopper(I) reagent 1[3] to the α,β-unsaturated aldehyde 9 delivered the 2-(trimethylstannyl)allyl group stereoselectively *cis* to the adjacent angular proton. Appropriate workup provided, in very good yield, an epimeric mixture of the aldehydes 10 and 11, in a ratio of

about 2.2:1. Iododestannylation of this material by treatment with *N*-iodosuccinimide (NIS) in dichloromethane gave a mixture of the corresponding alkenyl iodides **12** and **13**, which were readily separable by chromatography on silica gel. The isolated yields of **12** and **13** were 64 and 27%, respectively. Treatment of the minor diastereomer **13** with NaOMe in MeOH, followed by a second chromatographic separation of the resultant mixture (**12:13** ≈ 8:1) gave additional amounts of **12** (79% from pure **13**). Thus, the overall yield of **12** from **9** was 85%.
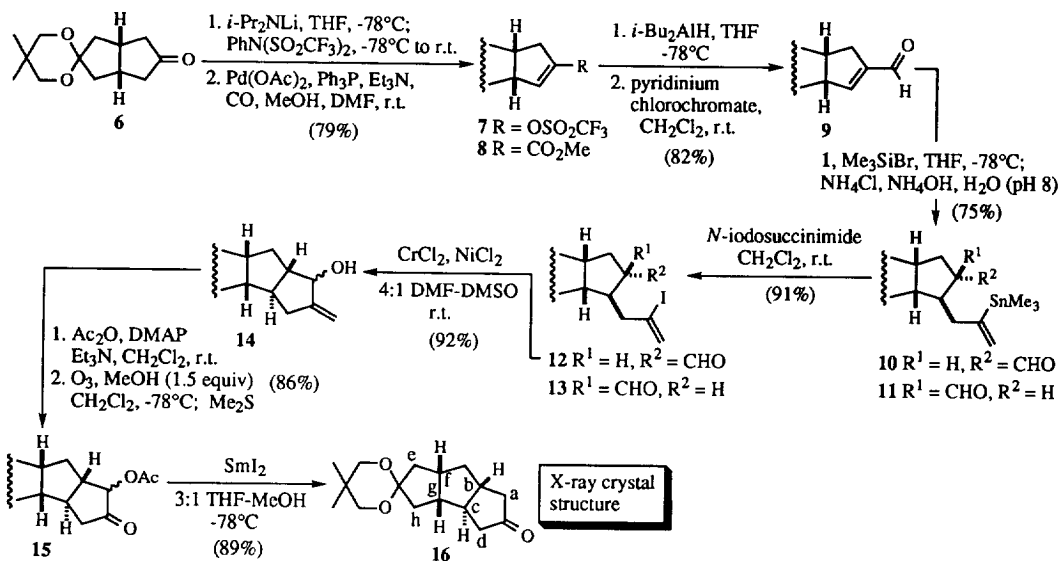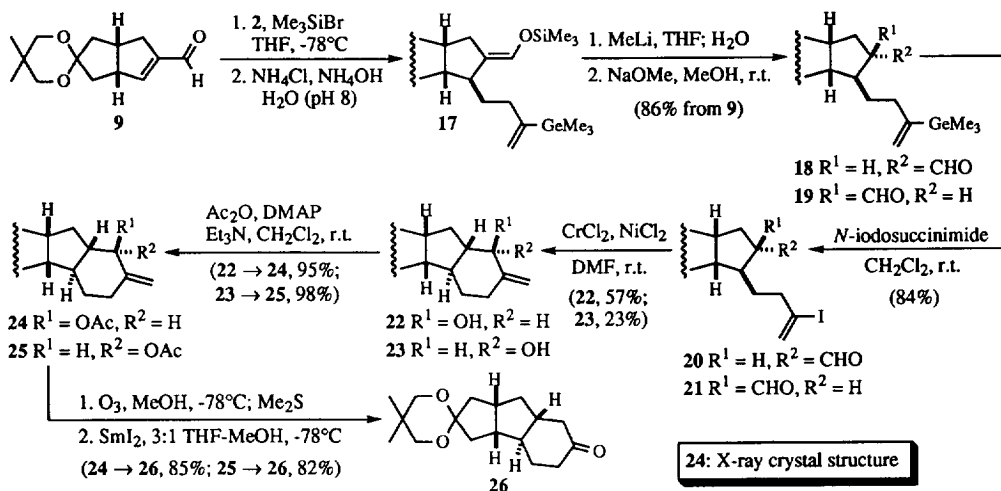

Scheme 1

Cyclization of the iodo aldehyde **12** could be carried out under very mild conditions and proved to be remarkably efficient. Treatment of **12** with chromium(II) chloride (6 equiv) in the presence of nickel(II) chloride (0.6 equiv)[9,10] in a 4:1 mixture of *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO)[11] for 30 minutes at room temperature produced **14** as a 1:1 mixture of epimeric alcohols (92% yield). This mixture, which was inseparable by chromatography on silica gel, was subjected to sequential acetylation and oxidative cleavage of the carbon-carbon double bond by ozonolysis. The resultant α-acetoxy ketone **15** (mixture of epimers) was produced in excellent yield. Samarium(II) iodide-mediated reductive removal of the α-acetoxy function[12] afforded a single crystalline product that exhibited a m.p. of 74-75°C after recrystallization from heptane. A single crystal X-ray structure determination established that this material possesses the constitution and relative configuration shown in structural formula **16**.[13,14] It should be noted that the acquisition of **14**, the corresponding acetate, and **15** as epimeric mixtures does not preclude the use of these substances as productive intermediates for other synthetic operations.

The effective utilization of the bifunctional cuprate reagent **2** for the construction of the *trans*-fused bicyclo[4.3.0]nonane ring system is outlined in **Scheme 2**. Conjugate addition of **2** to the aldehyde **9** in the presence of Me₃SiBr led to the isolation of the alkenyl trimethylsilyl ether **17**. Sequential treatment of a THF solution of the latter material with MeLi and water,[16] followed by equilibration (NaOMe, MeOH) of the resultant

products, afforded, in 86% yield from **9**, a mixture of the two epimeric aldehydes **18** and **19** in a ratio of 9:1. NIS-mediated iododegermylation[17] of this mixture gave the corresponding iodides **20** and **21** (9:1), which, upon treatment with $CrCl_2$-$NiCl_2$ in DMF,[10] provided primarily a chromatographically separable mixture of the epimeric allylic alcohols **22** and **23** (isolated yields of 57 and 23%, respectively).[19]

Scheme 2

Acetylation of each of the alcohols **22** and **23** provided **24** and **25**, respectively. An X-ray crystallographic study[13] involving the acetate **24** (m.p. 92-93°C, from heptane) established that the bicyclo[4.3.0]nonane unit in this substance is, as expected, *trans*-fused and that the major product derived from the ring closure of the iodo aldehyde **20** is the alcohol **22**, in which the newly formed hydroxyl function is *cis* to the adjacent angular proton. Oxidative cleavage of the exocyclic double bond of each of the allylic acetates **24** and **25**, followed by reductive expunction of the acetoxy group[12] from each of the products, gave excellent yields of the tricyclic keto ketal **26**.

Clearly, the new methodology described above could be employed in a wide variety of synthetic contexts and, in principle, similar strategies could be developed for the construction of *trans*-fused bicylic systems other than bicyclo[3.3.0]octanes and bicyclo[4.3.0]nonanes.

References and Notes

1. For an excellent recent report on a method for preparing *trans*-fused 5,6-, 5,7-, and 5,8-bicyclic ring systems and for a comprehensive list of references regarding earlier work in this general area, see Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B.; Postema, M. H. D. *J. Org. Chem.* **1993**, *58*, 6857.

2. For recent reports describing a number of interesting methods for the synthesis of *trans*-fused bicyclo[3.3.0]octane systems, see Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org.*

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7. All new compounds reported herein display spectra in accord with assigned structures and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high-resolution mass spectrometry).

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10. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

11. Use of DMF as the sole solvent[10] in this reaction gave inferior yields of **14**. In the intermolecular reactions reported by Kishi and coworkers,[9] DMSO was employed as the solvent. For the conversion of **12** into **14**, a 4:1 mixture of DMF-DMSO proved to be very satisfactory.

12. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

13. We are very grateful to Dr. Steven J. Rettig for carrying out this X-ray crystallographic study. Details of this structure determination will be disclosed elsewhere.

14. Interestingly, in the solid state, the torsion angles traced in going from C-a to C-d (via C-b and C-c) and from C-e to C-h (via C-f and C-g) (see structural formula **16**) are 44.5° and -4.8°, respectively. The significant strain energy associated with *trans*-fused bicyclo[3.3.0]octane systems is well known.[15]

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16. Attempted conversions of **17** into **18** + **19** by hydrolysis of the alkenyl trimethylstannyl ether with water or by cleavage of this function with Bu$_4$NF in THF did not produce satisfactory results. Details will be given in a full account of this work.

17. Iododegermylation with I$_2$ in CH$_2$Cl$_2$[18] caused partial, concomitant transfer of the OCH$_2$C(Me$_2$)CH$_2$O moiety from the ketal function to the aldehydic carbonyl group. Use of NIS precluded this side reaction. Subsequently, the latter protocol was also employed for the iododestannylation of the mixture of **10** and **11** (*vide supra*).

18. Oda, H.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 3221.

19. Also produced was a minor amount of a mixture of allylic alcohols resulting from ring closure of **21**.