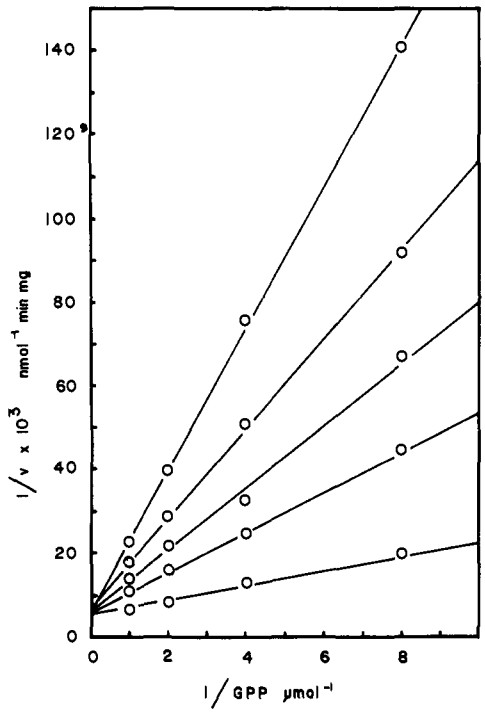

Figure 1. Inhibition of the enzyme with (*Z*)-3-OPP. Incubations were at 37 °C in 200 μL of 10 mM potassium phosphate buffer, pH 7.4, 1 mM $MgCl_2$, 0.1 mM dithiothreitol, 1 μM NaN_3, and 0.5 μM IPP with 26 ng of prenyltransferase and the indicated concentrations of GPP. Determinations were in duplicate. Concentrations of (*Z*)-3-OPP: none, 2.5, 5, 10, and 20 μM.

± 0.2 μM) suggest that 2-fluorogeranyl pyrophosphate is tightly bound by the enzyme. This observation is supported by inhibition kinetics, which show that (*Z*)-3-OPP is a *competitive inhibitor* (see Figure 1) of geranyl pyrophosphate with K_i = 2.4 ± 0.5 μM.

In summary, 2-fluorogeranyl pyrophosphate reacts with isopentenyl pyrophosphate in the presence of prenyltransferase to yield a C(15) fluorine containing homologue. The substrate analogue binds specifically to the allylic site, and kinetic behavior suggests that the binding is almost as tight as that of the natural substrate. Finally, replacing the C(2) hydrogen in the geranyl system by fluorine retards the rate of solvolysis, a reaction known to proceed through a carbonium ion intermediate, and the V_{max} of the prenyltransfer reaction by similar amounts.[25] We conclude that the head-to-tail coupling reaction catalyzed by prenyltransferase proceeds by an ionization-condensation-elimination mechanism. Experiments are underway in our laboratory to determine the timing of the individual steps.

References and Notes

(1) This investigation was supported by Grant GM 21328 from the National Institutes of Health.
(2) G. Popjak, *Annu. Rev. Biochem.*, **27**, 533 (1958).
(3) (a) H. C. Rilling and K. Block, *J. Biol. Chem.*, **234**, 1424 (1959); (b) J. W. Cornforth and G. Popjak, *Titrahedron Lett.* **No. 19**, 29, (1959).
(4) (a) G. Popjak and J. W. Cornforth, *Biochem. J.*, **101**, 553 (1966); (b) J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, **241**, 3970 (1966); (c) J. W. Cornforth, *Angew. Chem., Int. Ed. Engl.*, **7**, 903 (1968); (d) G. Popjak in "Natural Substances Formed Biologically from Mevalonic Acid", T. W. Goodwin, Ed., Academic Press, New York, N.Y., 1970, p 17; (e) G. R. Waller in "Progress in the Chemistry of Fats and Other Lipids", Vol. 10, R. T. Holman, Ed., Pergamon Press, New York, N.Y., 1970, pp 153–238; (f) T. W. Goodwin, *Biochem. J.*, **123**, 293 (1971).
(5) C. D. Poulter and H. C. Rilling, *Biochemistry*, **15**, 1079 (1976).
(6) We make the logical assumption that ionization or condensation is the slowest step during the prenyltransfer reaction.
(7) C. D. Poulter, D. M. Satterwhite, and H. C. Rilling, *J. Am. Chem. Soc.*, **98**, 3376 (1976). The experiments described for GPP were repeated with DMAPP and the results were similar.
(8) The pattern could result from binding of the C(5) substrate analogue to the isopentenyl site as well as the allylic site.
(9) F. G. Drakesmith, R. D. Richardson, O. J. Stewart, and P. Tarrant, *J. Org. Chem.*, **33**, 286 (1968).
(10) P. W. Holloway and G. Popjak, *Biochem. J.*, **104**, 57 (1967).
(11) Satisfactory IR and NMR spectra were obtained for all compounds. (*Z*)-2-OCH_3 and (*Z*)-3-OH gave satisfactory carbon–hydrogen analyses. Pyrophosphate (*Z*)-3-OPP gave a single spot on silica gel H plates (R_f 0.55 with $CHCl_3$/MeOH/H_2O 50:50:10). In the same solvent system the R_f's of geranyl phosphate and geranyl pyrophosphate were 0.72 and 0.54, respectively.
(12) In comparison the 3-methyl group in methyl (*E*)-geranate is deshielded by 0.25 ppm relative to the *Z* isomer.[13]
(13) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2886 (1960).
(14) Previously reported four-bond couplings between methyl protons and fluorine across a double bond do not give a consistent pattern.[15]
(15) G. J. Martin and M. L. Martin, *Prog. Nucl. Magn. Reson. Spectrosc.*, **8**, 163 (1972).
(16) The enzyme was from a sample that had been purified to homogenity (SA ~2000) before storage. We wish to thank Professor Hans Rilling for providing the enzyme and for helpful discussions.
(17) By 48 h the reaction had essentially stopped at two-thirds completion,[18] based on unreacted isopentenyl pyrophosphate. The enzyme was still active, and presumably the reaction stopped because of product inhibition.
(18) An acid lability assay[19] was used to follow the reaction.
(19) B. C. Reed and H. C. Rilling, *Biochemistry*, **14**, 50 (1975).
(20) We are now attempting to prepare enough material for a through NMR study.
(21) All incubations were at 37 °C in 10 mM potassium phosphate buffer with 1.0 mM magnesium chloride and 0.1 mM dithiothreitol, pH 7.4. Total volume was 200 μL.
(22) Kinetics were measured conductiometrically in 90% acetone/water, $k_{(Z)\text{-3-OMs}}^{60°C} = (2.29 \pm 0.03) \times 10^{-3}$, $k_{GOMs}^{0°C} = (1.74 \pm 0.07) \times 10^{-3}$, $k_{GOMs}^{25°C} = (2.47 \pm 0.03) \times 10^{-2}$ s^{-1}. Extrapolation to 60 °C gives $k_{GOMs}^{60°C} = 5.2 \times 10^{-1}$ s^{-1}.
(23) Our values for IPP and GPP are similar to those reported for the avian liver enzyme[19] and considerably below those previously reported for porcine liver farnesyl pyrophosphate synthetase.[10,24] The superscripts refer to the variable substrates and the subscripts to the fixed substrates in runs from which the Michaelis constants were determined.
(24) G. Popjak, P. W. Holloway, R. P. M. Bond, and M. Roberts, *Biochem. J.*, **111**, 333 (1969).
(25) The small difference of a factor of 5 in the retardations of the solvolytic and enzymatic reactions is not surprising in view of the obvious difference in local environments during ionization, the difference in leaving groups, and the observation that (*Z*)-3-OPP may bind slightly less tightly than GPP, $K_{IPP}^{GPP} = 0.8 \pm 0.02$ μM, while $K_{IPP}^{(Z)\text{-3-OPP}} = 1.1 \pm 0.2$ and $K_i = 2.4 \pm 0.5$ μM.
(26) (a) Alfred P. Sloan Fellow; (b) Career Development Award from the National Institutes of Health, HL00084.

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Formation of Fused, Spiro, and Metacyclophane Rings via Intramolecular Carbanion Attack on Arene–Chromium Complexes

Sir:

The activating effect of π-bonded transition metals in the addition of nucleophiles to arene ligands is well established.[1] Combined with mild oxidation of the intermediate η^5-(alkylcyclohexadienyl)chromium tricarbonyl anion,[2] this process has been shown in simple examples to be an efficient means of formal nucleophilic substitution for hydrogen.[3] Here we report intramolecular reaction of carbanions onto π-arene ligands which provide examples of more complex conversions appropriate for organic synthesis, unexpected examples of thermodynamic vs. kinetic control over ring size, and the formation of a [3.3]metacyclophane.

Successful intermolecular additions to π-benzenechromium tricarbonyl have been observed with carbanions stabilized by carboalkoxy,[3] nitrile,[3] sulfur,[3] keto,[4] and imino[4] units, as well as a few examples of simple organolithium reagents.[3,4] We find that ester enolates fail in intramolecular addition to π-arene ligands,[5] while the anion of 1,3-dithiane (and, presumably, anions derived from still less acidic carbon acids) cannot be generated efficiently by direct proton abstraction in the presence of a π-arene unit.[6] However, nitrile-stabilized anions, such

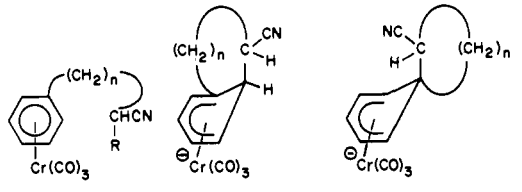
Table I. Change in Product Composition During Cyclization[a] of Complex **1a**

Time, h	Temp, °C	% **5a**[b]	% **6**	% yield[c] (combined)
0.5	−78	72	28	72
0.25	0	37	63	79
4.0	0	25	75	81
24	0	3	97	70

[a] The reactions were run in THF:HMPA (2:1) with acid quenching.[15] [b] The fraction **5a** includes all isomers of **5a** and is determined by relative GC, areas without all calibration with pure samples of the products. [c] The yield is based on material from short path distillation, shown to contain only **5a** (and isomers) and **6** by GC and ^{1}H NMR analysis, and through conversion of **5a** (and isomers) to **4a**.

as those derived from complexes **1a–d** undergo smooth cyclization.

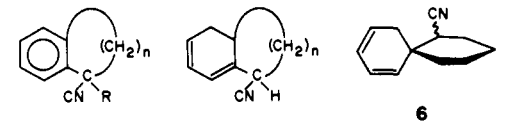
For example, complex **1b**[8] was prepared in 62% yield by simply heating at reflux a solution of chromium hexacarbonyl (4 mole equiv) and 5-phenylvaleronitrile in dioxane under argon with a large diameter air condenser.[9] The yellow solid complex has mp 41–43 °C, is easily handled in air, and is soluble in most organic solvents. Addition of a solution of complex **1b** in tetrahydrofuran (THF) to a solution of lithio-2,2,6,6-tetramethylpiperidide[11] (LiTMP, 1 mole equiv) in THF at −78 °C followed by stirring at 0 °C for 24 h afforded a yellow solution of η^5-cyclohexadienylchromium species. Oxidative quenching[12] led to isolation[13] of 1-cyanotetralin (**4b**) in 89% yield.[8,14] When the yellow solution (before oxidation) was quenched by protonation,[15] the product was a mixture of at least three olefin positional isomers (e.g., **5b**) of 1-cyanohexahydronaphthalene (100% yield). Treatment with dichlorodicyanoquinone (DDQ, 1 h, in benzene at 80 °C) produced **4b** as the only product, isolated in 84% yield overall from **1b**. Based on the intermediacy of η^5-(alkylcyclohexadienyl) complexes in intermolecular reactions,[2] the fused (**2b**) and spirocyclic (**3b**) species were considered reasonable intermediates during reactions of **1b**. The products (**4b, 5b**) suggest that **2b** is the exclusive intermediate. In the same way, the tertiary carbanion derived from **1d**[8] (LiTMP, THF, 0 °C, 4 h, oxidative quenching) produced 1-cyano-1-methyltetralin (**4c**)[8,16] in 87% yield.



1 a: n=4, R=H; b: n=3, R=H; c: n=2, R=H; d: n=3, R=CH_3

2 a: n=4; b: n=3; c: n=2

3 a: n=4; b: n=3; c: n=2



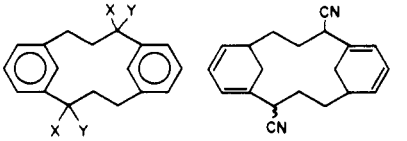
4 a: n=4, R=H; b: n=3, R=H; c: n=3, R=CH_3

5 a: n=4; b: n=3

6

With the higher homologue **1a**,[8] the site of ring closure appears to depend on the time and temperature used for formation of the η^5-cyclohexadienylchromium intermediates. Using hexamethylphosphoric triamide (HMPA) mixed with THF (1:2, v:v) as the medium, treatment of **1a** with 1 mole equiv of LiTMP for 0.5 h at −78 °C followed by oxidative quenching[12] produced the fused ring isomer **4a** (79% yield) as the only monomeric product. However, longer reaction time and/or higher temperature gave lower yields of **4a** and substantial amounts of high molecular weight products. With the alternative quenching procedure (acid[15]), high yields of monomeric products were observed under all conditions, consisting of **5a** (and olefin positional isomers)[17] and the spirocycles **6** (mixture of two diastereoisomers).[18] Table I indicates a smooth increase in the proportion of spirocycles **6** at longer reaction times. The simplest interpretation is formation of intermediate **2a** as the kinetic product followed by slow equilibration, via 1,2-carbon shift, to the thermodynamically more favorable product, **3a**.[19] Oxidative quenching requires rearomatization of the η^5-cyclohexadienylchromium intermediate which does not occur smoothly from **3a**.

With the lower homologue **1c**,[8] both the spirocyclic (i.e., **3c**) and fused (i.e., **2c**) intermediates appear to be unfavorable. Treatment of **1c** with lithium diisopropylamide at 0 °C in THF followed by oxidative quenching[12] gives a single product, isolated in 84% yield after one recrystallization (mp 153–154.7 °C). The product proved to be dimeric and has been tentatively assigned the structure **7**, a [3.3]metacyclophane.[8,20] Since this appears to be the first reported example of a carbocyclic [3.3]metacyclophane,[21] a simple degradation was carried out via oxidative decyanation[22] to the corresponding diketone **8** (68% yield, mp 134–136 °C).[8,20] Then Bayer-Villegar oxidation followed by hydrolysis and methylation (methyl ether and methyl ester) produced a single product, methyl *m*-(2-methoxyethyl)benzoate, identified by comparison with a commercial sample. Acid quenching[15] (instead of oxidation) led to a dihydroaromatic analogue (e.g., **9**).[8,20] The tetrahydrometacyclophane (**9** or an olefin positional isomer) was resistant to dehydrogenation, but treatment with DDQ (24 h, 80 °C) eventually produced **7** (82% yield).

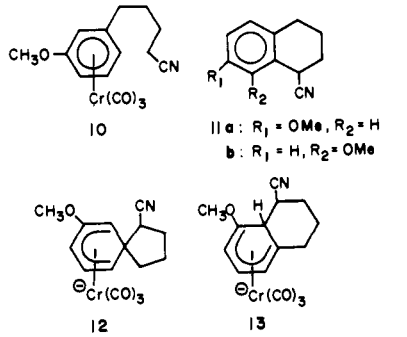


7: X=H, Y=CN

8: X, Y=O

9

Complex **10**, bearing a methoxy substituent, was prepared in 46% yield (after column chromatography) in the usual way from 4-(3-methoxyphenyl)butyronitrile. Treatment with lithium diisopropylamide at 0 °C in THF for 4 h followed by oxidative quenching[12] produced a mixture (90% yield) of two 1-cyanomethoxytetralin isomers (**11**) in a 60:40 ratio. The positions of the methoxyl substituents were confirmed through oxidative decyanation[22] to 7-methoxy-1-tetralone and 8-methoxy-1-tetralone which were identified by comparison of GC retention times and ^{1}H NMR and mass spectra with corresponding data from commercial samples of 5-, 6-, and 7-methoxy-1-tetralones and 8-methoxytetralone from unam-



10

11a: R_1 = OMe, R_2 = H; b: R_1 = H, R_2 = OMe

12

13

biguous synthesis.[23] The formation of 1-cyano-7-methoxytetralin (**11a**) is most simply rationalized by a 1,2-alkyl shift in the spirocyclic intermediate **12** during oxidative quenching. The other isomer (**11b**) could arise from 1,2-cyanoalkyl migration in **12**, or from direct oxidative quenching of the fused ring intermediate, **13**.

Studies are in progress to further define the scope of the intramolecular carbanion additions to π-arene ligands and to understand the factors which influence ring size preferences.[24]

References and Notes

(1) For examples, see (a) B. Nicholls and M. C. Whiting, *J. Chem. Soc.*, 551 (1959); (b) J. F. Helling and G. G. Cash, *J. Organomet. Chem.*, **73**, C10 (1974); (c) A. Nesmeyanov, N. Volkenaw, and J. Balesova, *Tetrahedron Lett.*, 1725 (1963); (d) P. J. C. Walker and R. J. Mawby, *Inorg. Chim. Acta*, **7**, 621 (1973).

(2) These intermediates have been observed directly: M. F. Semmelhack, M. Yoshifuji, and H. T. Hall, Jr., *J. Am. Chem. Soc.*, **98**, 6387 (1976).

(3) M. F. Semmelhack, H. T. Hall, Jr., M. Yoshifuji, and G. Clark, *J. Am. Chem. Soc.*, **97**, 1247 (1975).

(4) Results, by G. Clark at Cornell, to be submitted for publication.

(5) Analogues of complexes **1a–c** where the –CN unit is instead $-CO_2R$ (R = Me, *t*-Bu) failed to give cyclization (enolate anion generated with lithium diisopropylamide, iodine oxidation[3]). High molecular weight material, presumably formed through intermolecular attack of the enolate anion on an arene ligand, comprised the product.

(6) Preliminary experiments with analogues of complexes **1a–c** where the $-CH_2CN$ unit is replaced by the 1,3-dithian-2-yl unit failed to show more than small amounts of intramolecular attack. Important side reactions include proton abstraction from the arene ring (*n*-butyllithium as base).[7]

(7) Cf. (a) A. Nesmeyanov, N. E. Kolobova, K. N. Anisimov, and Yu. V. Marakov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2665 (1968); (b) R. J. Card, PhD Thesis, Iowa State University, 1974.

(8) Satisfactory ^{1}H NMR, IR, and low resolution mass spectral data have been obtained for this compound.

(9) The air condenser is a 60-cm glass tube with $\overline{\text{T}}$ joints placed in one neck of the reaction vessel and capped with a stopcock for introduction of argon. The solvent condenses on the air-cooled surface and carries back most of the rapidly subliming chromium hexacarbonyl. This arrangement is effective and simpler than the Strohmeier apparatus.[10]

(10) W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1976).

(11) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 582 (1973).

(12) Oxidative quenching involves addition of a solution of excess iodine in THF at −78 °C followed by warming at 25 °C for 4–8 h.

(13) The mixture was diluted with ether, washed sequentially with sodium thiosulfate solution, aqueous acid, and saturated salt solution, dried, and concentrated at reduced pressure. Short path distillation at ca. 100°/0.01 Torr afforded the product in >98% purity (GC, ^{1}H NMR).

(14) Hydrolysis (30% hydrogen peroxide, sodium hydroxide, 95% ethyl alcohol) produced the corresponding primary amide, mp 167–169 °C. Lit mp 165–167 °C (J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962)).

(15) The acid quenching involved cooling the solution of the η^5-cyclohexadienylchromium intermediate to −78 °C, adding 5 mole equiv. of trifluoroacetic acid, and allowing the mixture to stir at 0–25 °C for a few hours. Then excess iodine was added to cleave all organochromium π-complexes and isolation of the organic products proceeded as before.[12,13]

(16) The structure of **4c** was established by comparison of GC, ^{1}H NMR, and IR data with the same compound derived from intramolecular carbanion addition to a benzyne intermediate. Cf. R. W. Hoffman, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, N.Y. 1967.

(17) Treatment of the mixture of isomers related to **5a** with DDQ in benzene at 80 °C for 1 h afforded the aromatic derivative **4a** in quantitative yield.

(18) The pair of diastereoisomers was separated by preparative GC. Satisfactory UV, IR, ^{1}H NMR, and mass spectral data were obtained for each isomer.

(19) Migration of the carbanion unit from one position to another in the η^5-cyclohexadienyl intermediate is also observed in intermolecular cases: M. Yoshifuji and G. Clark, unpublished observations at Cornell.

(20) Satisfactory combustion analysis was obtained for this compound.

(21) The heterocyclic analogue, 2,11-dithia[3.3]metacyclophane, is well known: Cf. R H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, **96**, 1547 (1974).

(22) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975).

(23) We are indebted to Professor G. Marc Loudon for spectral data from 8-methoxy-1-tetralone.

(24) We are pleased to acknowledge support of the National Science Foundation through Grant CHE76-01112.

(25) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Grant, 1973–1978.

(26) Visiting Professor, summer 1975 and 1976.

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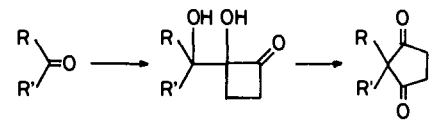
Geminal Acylation via Pinacol Rearrangement. Synthesis of Spiro[4.*n*] Ring Systems

Sir:

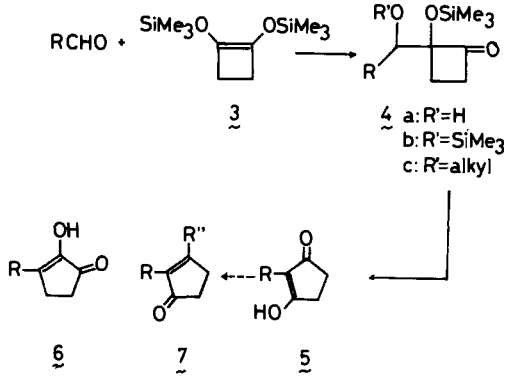
In connection with syntheses of naturally occurring products with cyclopentenone[1] and spiro[4.5]decane rings,[2] considerable efforts have recently been directed to the construction of five-membered rings. In this respect, we focused our attention on 1,3-cyclopentanedione derivatives, for they are versatile precursors of fused ring systems,[3] as well as those of various functionalized five-membered rings, e.g., cyclopentenone.[1] Pinacol rearrangement driven by the release of the ring strain of a four-membered ring[4] was envisioned to provide a way to this end. Further, we expected that the rearrangement of the pinacol **1** may be controlled by the presence of an acyl group adjacent to the diol moiety to give the 1,3-cyclopentanedione **2**. The reaction proceeded, indeed, as depicted below. This two-step sequence represents a new annelation method as well as a geminal acylation[5] approach to cyclopentanediones.



1 **2**

Bis-silylated succinoin, **3**,[6] the starting material of pinacol **1**, was prepared by acyloin condensation of a succinate in the presence of chlorosilane. It seems expedient that a variety of the four-membered acyloin derivatives are available from the products of Stobbe condensation and Diels–Alder reaction of fumalates and maleates.[6b]

Preparation of the pinacol was achieved either by Lewis acid-mediated aldol addition[7] or by a fluoride catalyzed one,[8] in which the pinacol was isolated as a silylated form, **4**.[9] The reaction of **3** and benzaldehyde at −78 °C gave **4a** (R = Ph), in 78% yield with $TiCl_4$, and **4b** (R = Ph), in 75% yield with tetrabutylammonium fluoride (TBAF).[10] Treatment of the aldol adduct **4** with trifluoroacetic acid (TFA) at room temperature afforded the cyclopentanedione **5** in high yield (Table I, entries 1 and 2). None of the isomeric products like **6** was isolated. 1,3-Cyclopentanedione thus prepared can be transformed to 2,3-disubstituted cyclopentenone **7** by an established procedure.[11]



3 **4** a: R'=H, b: R'=$SiMe_3$, c: R'=alkyl

6 **7** **5**

Since an acetal coordinates with Lewis acids more strongly than its parent carbonyl compound, and is often a primary product of the recent synthetic methods of carbonyl function,[12] it appeared to be a reaction partner of choice, rendering this annelation method more effective. In fact, the aldol reaction mediated by BF_3·Et_2O or $TiCl_4$[13] proceeded nicely with acetals. The reaction conditions are mild (−78 °C) and did not cause loss of the trimethylsilyl group of the adduct **4c**.[9]

Application of this annelation method to ketals provides a