Stereocontrol of Three Contiguous Chiral Centers of Brassinosteroid Side Chain Using α-Alkoxy Organoleads

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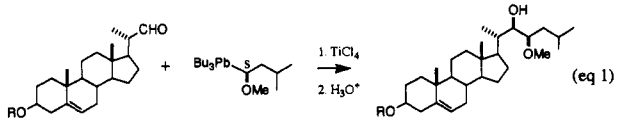
Summary: The reaction of steroidal aldehyde **2** with chiral α-methoxyorganolead (*S*)-**3** in the presence of $TiCl_4$ gave the Cram-syn product **4**, a precursor of 28-norbrassinolide, in 90% yield as a single stereoisomer. A kinetic resolution was observed in the $TiCl_4$ mediated reaction of **2** with (±)-**3**; again **4** was produced in 99% yield as a single isomer.

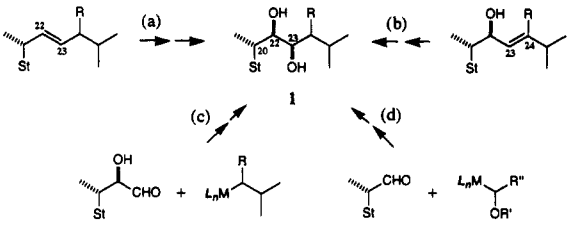
A number of useful synthetic methods for the side chain of brassinosteroids **1**, plant growth regulator, have been reported.[1] One of the most important problems for the construction of the side chain seems to be the production of two syn hydroxy groups at C-22 and C-23. Until now, there have been reported four approaches (Scheme I): (a) osmylation or epoxidation–ring opening of the $\Delta^{22(23)}$ double bond derivative,[2] (b) epoxidation–ring opening of the $\Delta^{23(24)}$ double bond derivative,[3] (c) the reaction of organometallic compounds with the C-22 hydroxy aldehyde,[4] and (d) the reaction of α-oxygen-substituted organometallic reagents with an easily available steroidal aldehyde.[5] The last method has been studied extensively in recent years. 2-Lithiofuran derivatives[5a–d] and (γ-methoxyallyl)tin[5e] were used as an α-oxo-substituted organometallic reagent. We report a new approach to this problem: the reaction of steroidal aldehyde **2** with chiral α-methoxy organolead (*S*)-**3** in the presence of $TiCl_4$ gave **4** in 90% isolated yield as a single isomer (eq 1).



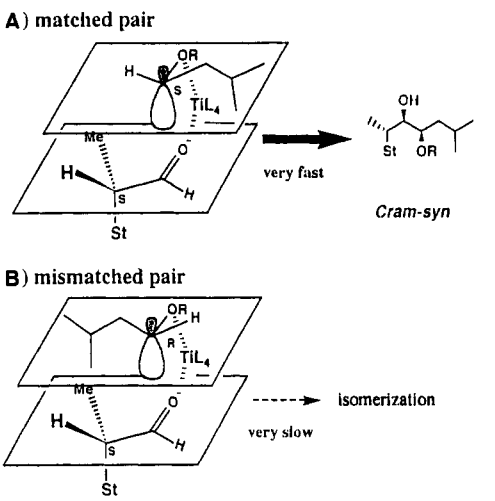
2 R=t-BuMe$_2$Si (S)-3 4 90% yield single isomer (eq 1)

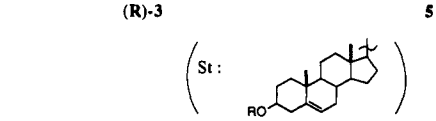
We previously reported that the reaction of tetraalkyllead compounds with 2-phenylpropanal in the presence of $TiCl_4$ produced the *Cram isomer* with high diastereoselectivity.[6] Later on, we found that the $TiCl_4$-mediated reaction of α-alkoxy organolead reagents with simple aldehydes, such as benzaldehyde and octanal, *gave syn-1,2-diol derivatives* with nearly 100% diastereoselectivity.[7] The stereochemical relationship among C-20, -22, and -23 of **1** is "Cram-syn", if procedure d for C–C bond formation is counted. Accordingly, it occurred to us that the reaction of chiral aldehyde **2** with certain chiral α-alkoxy organolead reagents may give **1** having Cram-syn stereochemistry. In fact, the reaction of **2** with 2 equiv of (*S*)-**3** in the presence of $TiCl_4$ gave **4** as a single isomer in 90% yield (eq 1).[8] No stereoisomers were detected. On the other hand, the reaction of **2** with 2 equiv of (*R*)-**3** afforded a 1:2 mixture of **4** and **5** in only 22% yield (eq 2). Apparently, the latter is a mismatched combination and (*R*)-**3** reagent undergoes isomerization to (*S*)-**3**

Scheme I. Four Routes to the Side Chain of Brassinosteroids



Scheme II





(eq 2)

(1) For reviews, see: Chen, S. C. *Chem. Can.* **1983**, *35*, 13. Mori, K. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 849.

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(3) (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (b) Ishiguro, M.; Takatsuto, S.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (c) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. I* **1984**, 139. (d) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767. (e) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491. (f) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1984**, *49*, 4297. (g) Takahashi, T.; Ootake, A.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 69. (h) Mori, K.; Sakakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767.

(4) (a) Takatsuto, S.; Ikekawa, N. *Tetrahedron Lett.* **1983**, *24*, 773; *J. Chem. Soc., Perkin Trans. I* **1983**, 2133.

(5) (a) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2833. (b) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055. (c) Kametani, T.; Katoh, T.; Fujio, J.; Nogiwa, I.; Tsubuki, M.; Honda, T. *J. Org. Chem.* **1988**, *53*, 1982. (d) Honda, T.; Keino, K.; Tsubuki, M. *J. Chem. Soc., Chem. Commun.* **1990**, 650. (e) Koreeda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143.

(6) Yamamoto, Y.; Yamada, J. *J. Am. Chem. Soc.* **1987**, *109*, 4395.

(7) Yamada, J.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118.

(8) Excess amounts of the lead reagent were normally used. With an equivalent amount of (*S*)-**3**, the chemical yield was in a range of 75–85% and **4** was obtained as a single isomer.

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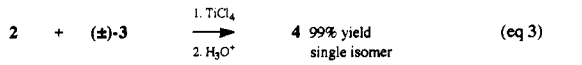
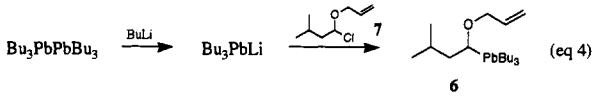
prior to the C–C bond formation. These findings suggested that a kinetic resolution would take place in the reaction of a chiral aldehyde with racemic **3**. The reaction of **2** with 4 equiv of (±)-**3** in the presence of $TiCl_4$ produced **4** as a single isomer in 99% yield (eq 3).



It is established that the reaction of (α-methoxyethyl)tributyllead with benzaldehyde in the presence of $TiCl_4$ proceeds through an S_E2-retention pathway and the aldehyde attacks the carbon attached to lead from the same side as the C–Pb bond (front side attack).[7] Accordingly, the S–S combination shown in eq 1 is a matched pair since sterically demanding isobutyl and steroidal groups can be oriented away from each other (Scheme II (A)). There exist little or no unfavorable steric interactions, and the reaction proceeds rapidly at low temperatures to give the Cram-syn isomer. In contrast, the *S–R* combination in eq 2 suffers from a severe steric interaction between the isobutyl and steroidal group (Scheme II (B)), since chelation by $TiCl_4$ forces these two substituents to orient in the same direction. The reaction must be very sluggish, leading to isomerization from (*R*)-**3** to (*S*)-**3**.

Being stimulated by this success on the stereocontrol of three contiguous chiral centers, we examined demethylation of the MeO group of the side chain of **4**. However, several attempts using typical demethylation procedures[9] resulted in failure. α-Allyloxy organolead **6**, in which the allyloxy group was thought to be more easily removable than the methoxy group, was prepared by the reaction of (tributylplumbyl)lithium with α-chloro ether **7** (eq 4). Previously, α-alkoxy organolead compounds were



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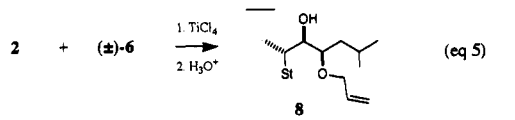
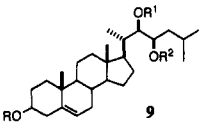
prepared by the transmetalation from the corresponding α-alkoxy tins.[7] However, this procedure is cumbersome and a new method shown in eq 4 is more convenient and of wide applicability.[10] (Tributylplumbyl)lithium,[11] prepared from hexabutyldiplumbum according to the reported procedure, was reacted with α-allyloxy chloride **7** in THF at −78 °C and then at 0 °C for 3 h to give **6** in 61% yield. The reaction of **2** with 4 equiv of (±)-**6** in the presence of $TiCl_4$ produced a mixture of 25% yield of **8** (R = TBDMS) and 11% yield of **8** (R = H, the deprotected product of the steroidal ring OR) along with the recovered **2** (50%) (eq 5).[12] Protection of both OH groups at C-22 and at C-3



of **8** (R = H) with MOMCl gave **9a** in an essentially quantitative yield. Selective hydroboration of the allyloxy double bond with thexylborane, followed by the usual oxidation with H_2O_2–NaOH produced **9b**, which was oxidized with PCC to give the aldehyde **9c**. Retro-aldol cleavage of the resulting β-oxo aldehyde **9c** with K_2CO_3/CH_3OH afforded the deprotected **9d** in 31% yield based on **9a**. Removal of the MOM protection with 12 M HCl/CH_3OH gave **9e**, a precursor of 28-norbrassinolide, as a colorless crystal in 80% yield, mp 188–189 °C (lit.[3c] mp 187–191 °C).[13]

Now, we are in a position to control the three contiguous chiral centers of steroidal side chains via one-step C–C bond formation. The next problem is to control the stereochemistry at C-24, the fourth chiral center. We are actively pursuing the research to solve this problem.



9a; R = R¹ = MOM, R² = $CH_2CH{=}CH_2$
b; R = R¹ = MOM, R² = $CH_2CH_2CH_2OH$
c; R = R¹ = MOM, R² = CH_2CH_2CHO
d; R = R¹ = MOM, R² = H
e; R = R¹ = R² = H

Supplementary Material Available: Synthesis of (±)-, (*R*)-, and (*S*)-**3**, the procedure for the reaction of **2** with **3** and **6**, the synthesis of **6**, the conversion of **8** to **9e**, and the spectral data of the products (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) (a) $EtSH/AlCl_3/CH_2Cl_2$/0 °C: Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97. (b) $HSCH_2CH_2SH/BF_3OEt_2$/120 °C: Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin Trans. I* **1976**, 2237.

(10) The details of the new synthesis of α-alkoxy leads and their application to organic synthesis will be reported shortly.

(11) Willemsens, L. C.; Van der Kerk, G. J. M. *J. Organomet. Chem.* **1968**, *15*, 117.

(12) The reaction of **6** was slower than that of **3**, and therefore decomposition of **6** by $TiCl_4$ competed with the desired coupling reaction upon warming the mixture from −75 °C to room temperature. The length of the reaction time for **6** was 12 h, same as that for **3**. If a prolonged reaction at lower temperatures and a precise temperature control were employed, an optimum yield would be obtained.

(13) A standard deallylation method using 10% Pd–C/MeOH–H_2O/*p*-TsOH/reflux was also used for **9a**, but a number of products were obtained: Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558.