Experimental Section

Materials and methods used were as described previously.[4]

Recovery of Fatty Acids. The methanolic potassium carbonate extract remaining from the preparation of 4 was slowly acidified under nitrogen with 170 mL of 3 M sulfuric acid. The oil was extracted with 1:1 ether–hexane (3 × 250 mL). The combined ether–hexane solutions were washed with water (2 × 200 mL) and brine (200 mL), dried, and evaporated to give 30.7 g of polyunsaturated fatty acids.

Iodolactonization. The fatty acids were dissolved in 530 mL of THF in a 2-L flask. A solution of 25 g (0.25 mol) of potassium bicarbonate and 38 g (0.23 mol) of potassium iodide in 265 mL of water was added with stirring. After 15 min, iodine (118 g, 0.46 mol) was added. The flask was sealed under nitrogen and stirred in the dark at 4 °C for 48 h. The mixture was poured slowly into a solution of 194 g (1.94 mol) of potassium bicarbonate and 145 g (0.92 mol) of potassium sulfite in 700 mL of water. The mixture was extracted with ethyl acetate (2 × 270 mL), and the extracts were evaporated. The residue was dissolved in 1170 mL of hexane and extracted with 580 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was promptly back extracted with 580 mL of 1:1 hexane–ether. The combined hexane–ether solutions were washed with water (3 × 260 mL) and brine (260 mL) and evaporated. The residue was applied to a bed of silica gel (230–400 mesh, 7 cm × 7 cm) and filtered under pressure with 1600 mL of 1:1 dichloromethane–hexane. Evaporation gave 11.1 g of a mixture of 3 and 4.

Eicosapentaenoic Acid (1). A solution of 11.1 g of 3 and 4 in 150 mL of acetonitrile was dried for 1 h over 4A molecular sieves and then added to a solution of 16.9 g (0.11 mol) of sodium iodide in 100 mL of acetonitrile in a 1-L three-neck flask fitted with a nitrogen purge and septum inlet. 2-Methyl-2-butene (4.77 mL, 45 mmol) was added, followed by chlorotrimethylsilane (3.80 mL, 30 mmol). The mixture was stirred at 22 °C for 2 h. TLC analysis (CH_2Cl_2) of the mixture revealed a steady decrease in the amount of 3 present in the mixture, with 4 remaining unaffected. The reaction was stopped by the addition of a solution of 3.8 g (30 mmol) of sodium sulfite and 3.5 g (12 mmol) of sodium citrate in 350 mL of water. The mixture was extracted with 4:1 hexane–dichloromethane (3 × 100 mL), and the combined extracts were washed with water (5 × 100 mL) and brine (100 mL) and concentrated. The crude product was taken up in 340 mL of hexane and extracted with 170 mL of 0.5 M potassium carbonate in 1:1 methanol–water. The alkaline solution was washed with 1:1 hexane–ether (2 × 70 mL) and then acidified under nitrogen with 50 mL of 4.5 M hydrobromic acid. The product was extracted with 2:1 hexane–ether (3 × 50 mL). The extracts were washed with water (3 × 30 mL) and brine (30 mL), dried, and evaporated to give 3.50 g of pure EPA (1): IR (NaCl) 1710 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 10 H, olefinic H), 2.84 (m, 8 H, 7-, 10-, 13-, 16-CH_2), 2.37 (t, 2 H, 2-CH_2), 2.12 (m, 4 H, 4- and 19-CH_2), 1.71 (m, 2 H, 3-CH_2), 0.97 (t, 3 H, 20-CH_3); FAB MS, m/z (relative intensity) 303 (MH^+, 2.4).

Methyl Eicosapentaenoate. A 101-mg (330-μmol) sample of 1 was dissolved in 7 mL of distilled ether and cooled to 0 °C. A slow stream of diazomethane in nitrogen (prepared by bubbling nitrogen through ethereal diazomethane) was passed into the sample until the esterification was complete. Drying, filtration, and evaporation gave 97 mg (93%) of methyl eicosapentaenoate: IR (NaCl) 1745 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (m, 10 H, olefinic H), 3.67 (s, 3 H, OCH_3), 2.84 (m, 8 H, 7-, 10-, 13-, 16-CH_2), 2.32 (t, 2 H, 2-CH_2), 2.10 (m, 4 H, 4- and 19-CH_2), 1.70 (m, 2 H, 3-CH_2), 0.97 (t, 3 H, 20-CH_3); CI MS (70 eV), m/z (relative intensity) 317 (MH^+, 100), 285 (17); GC (OV-1) (oven 180 °C) t_R 6.27 min, 95%. A sample of the methyl ester was hydrogenated with platinum in methanol; it was found to be identical with authentic methyl eicosanoate by GC analysis.

Acknowledgment. We thank Elaine Y. Kuo for assistance in preparing the EPA-enriched fatty acids.

Registry No. 1, 10417-94-4; 2, 6217-54-5.

Communications

A Novel Lanthanide-Induced Rearrangement

Summary: Treatment of α-hydroxy ketone 4 with samarium diiodide led to tricyclic alcohol 6 in high yield. Two intermediates in this process, α-hydroxy ketone 7 and ketone 8, have been isolated and identified. This process combines a Lewis acid (Sm^{3+}) mediated ring expansion with reductive loss of a hydroxyl substituent and transannular ketyl cyclization. The stereoelectronic features that make these transformations favorable are discussed in detail.

Sir: There has recently been great interest in the development and use of lanthanide-based reagents in organic synthesis.[1] In addition to their now traditional use as NMR shift reagents,[2] lanthanides have been shown to serve as catalysts for Diels–Alder reactions,[3] to provide interesting selectivity in various reductions and oxidations,[4] and to present an alternative to Grignard reagents and alkali metal enolates in additions to carbonyl compounds.[5] Although a theme common to these applications is the Lewis acidity of the lanthanide reagents, relatively few examples of lanthanide-induced rearrangements have been documented.[6] We now report a novel samarium-induced rearrangement–reduction–reductive cyclization, which we

(1) Reviews: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (b) Long, J. R. *Aldrichimica Acta* **1985**, *18*, 87.

(2) Cockerill, A. F.; Davies, G. L. O.; Harden, R. C.; Rackham, D. M. *Chem. Rev.* **1973**, *73*, 553.

(3) (a) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761. (b) Danishefsky, S.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1984**, *106*, 2453.

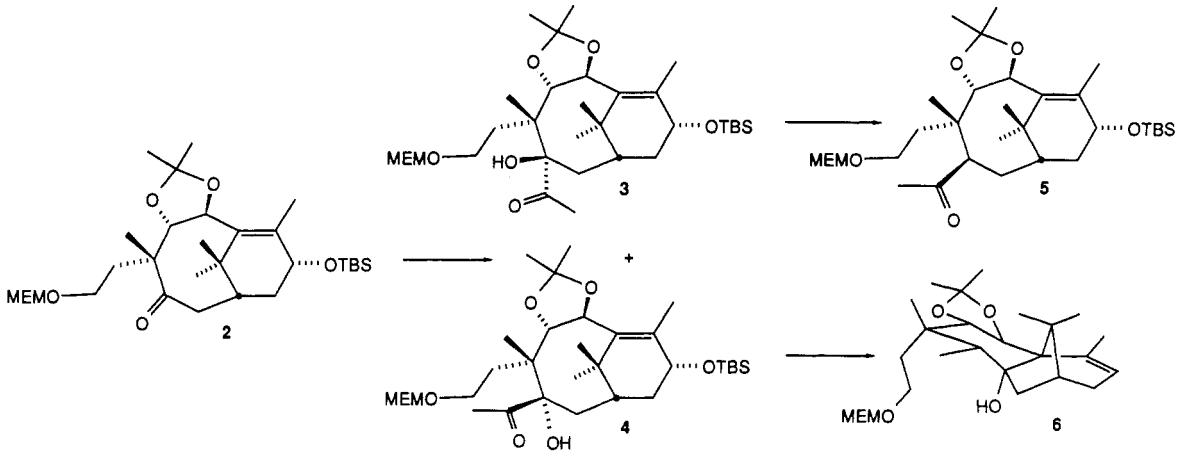
(4) See, for example: (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Marchand, A. P.; Laroe, W. D.; Madhaua, G. V.; Chanderswuri, S.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622. (c) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (d) Collin, J.; Namy, J. L.; Kagan, H. B. *Nouv. J. Chim.* **1986**, *10*, 2329. (e) Ho, T. L. *Synthesis* **1973**, 347. (f) Beletskaya, I. P.; Makhon'kou, D. I. *Russ. Chem. Rev.* (*Engl. Transl.*) **1981**, *50*, 534. (g) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (h) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.

(5) See, for example: (a) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556. (b) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (c) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4223. (d) Kauffman, T.; Pahde, C.; Tannert, A.; Wingbermuhle, D. *Tetrahedron Lett.* **1985**, *26*, 4063. (e) Fukuzawa, S.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1985**, 777.

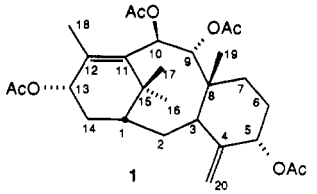
(6) The rearrangement of terminal epoxides is an exception to this generalization; see: Prandi, J.; Namy, J. L.; Menoret, G.; Kagan, H. B. *J. Organomet. Chem.* **1985**, *285*, 449.

0022-3263/88/1953-5981$01.50/0

Scheme I



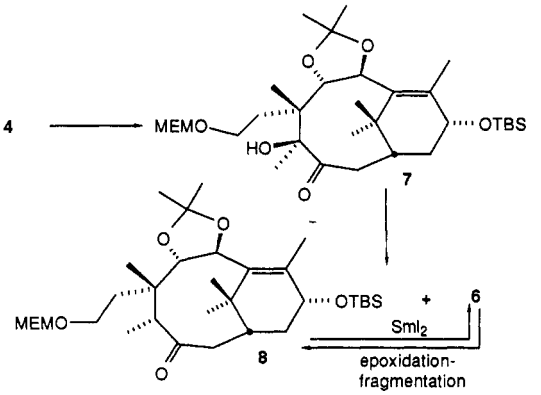
encountered during the course of our synthesis of taxusin (1).[7]



Addition of (α-methoxyvinyl)lithium to ketone **2**[7] (THF, −13 °C, 12 h) followed by in situ hydrolysis (2:1:1, THF/HOAc/H_2O) gave a 1:1 mixture of epimeric hydroxy ketones **3** and **4** in 90% yield. These were separated by silica gel chromatography and independently subjected to samarium diiodide reduction. As shown in Scheme I, hydroxy ketone **3**, a taxusin intermediate,[7] was smoothly reduced to ketone **5**. However, ketol **4**, $[\alpha]^{25}_{Hg}$ −109° ($CHCl_3$,*c* 1.02),[8,9a] upon treatment with samarium diiodide (10 equiv, THF, 25 °C, 2 h), was converted (92%) to a tertiary alcohol, $[\alpha]^{25}_{Hg}$ −63° ($CHCl_3$,*c* 0.29), which was assigned structure **6**[8] on the basis of spectral data.[9b]

Under milder conditions (3 equiv SmI_2, THF, 0 °C, 1 h), ketol **4** reacted to provide a different substance in 90% yield, which, again on the basis of spectral data,[9c] was assigned structure **7**,[8] mp 124–127 °C, $[\alpha]^{25}_{Hg}$ −70° ($CHCl_3$,*c* 0.23). It was readily apparent from the mass spectrum that the empirical formula of **7** was the same as that of **4** and that no reduction had taken place. Upon resubjection to samarium diiodide (10 equiv, THF, 0 °C, 2 h), ketol **7** was converted to a mixture consisting of small amounts of **7** and **6** and 70% of a new compound, **8**,[8,9d] $[\alpha]^{25}_{Hg}$ −66° ($CHCl_3$,*c* 0.24), the product of deoxygenation of **7**. Further treatment of **8** with samarium diiodide produced **6** in almost quantitative yield. Furthermore, tertiary alcohol **6** could be converted back to **8** in 90% yield by epoxidation and fragmentation[7,10] (CH_3CO_3H, CH_2Cl_2, 25 °C, 1 h; $Ti(OiPr)_4$, CH_2Cl_2, reflux, 20 h; TBSOTf, pyridine). These observations are summarized in Scheme II.

Scheme II



We propose the following rationale for these events. The rearrangement of **4** to **7** is a Lewis acid (presumably Sm^{3+}) mediated process. In the presence of Sm^{3+} alone under three different sets of conditions, **4** rearranged quantitatively to **7**. The rate of rearrangement was dependent upon the method of preparation of Sm^{3+} (SmI_2, O_2, THF, 25 °C, 24 h; SmI_2, cyclohexene oxide, THF, 0 °C, 2 h; SmI_2, *t*-BuOO-*t*-Bu, THF, 0 °C, 2 h, 50% conversion), and the formulation of the active Sm^{3+} species remains undetermined at this time.[11] The conformation of **4** is presumably (supported by NOE studies) one in which the hydroxyl group is in the plane of the carbonyl group, and the migrating bond is parallel to the p orbitals of the carbonyl group. From this conformation, ring expansion would be stereoelectronically favored over reduction, and furthermore, ring expansion should produce only the observed stereoisomer **7**. When **4** was treated with SmI_2 in the

(7) Holton, R. A.; Juo, R. R.; Kim, H. B.; Williams, A. D.; Harusawa, S.; Lowenthal, R.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

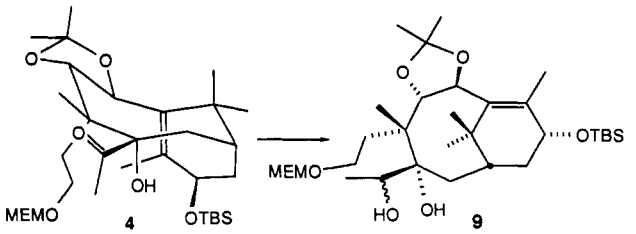
(8) Characterized by full spectral data (^1H NMR,[9] IR, ^{13}C NMR, MS) and HRMS or elemental analysis.

(9) ^1H NMR data (270 MHz, $CDCl_3$) for **4** and **6–8**: (a) (**4**) δ 4.80 (1 H, d), 4.69 (2 H, s), 4.67 (1 H, d), 4.59 (1 H, s), 4.28 (1 H, br d), 4.03 (1 H, m), 3.67 (3 H, m), 3.54 (2 H, m), 3.36 (3 H, s), 2.60 (1 H, m), 2.23 (3 H, s), 2.02 (2 H, m), 1.92 (3 H, s), 1.71 (3 H, s), 1.60–1.80 (2 H, m), 1.42 (3 H, s), 1.41 (3 H, s), 1.15–1.30 (2 H, m), 0.98 (3 H, s), 0.89 (9 H, s), 0.84 (3 H, s), 0.11 (3 H, s), 0.08 (3 H, s); (b) (**6**) δ 5.64 (1 H, br s), 4.70 (2 H, s), 4.33 (1 H, d), 3.91 (1 H, m), 3.81 (1 H, d) 3.67 (2 H, m), 3.61 (1 H, m), 3.55 (2 H, m), 3.38 (3 H, s), 2.42 (1 H, br d), 2.33 (1 H, ddd), 2.16 (1 H, m), 1.90 (3 H, s), 1.88 (1 H, br d), 1.74 (1 H, m), 1.56 (2 H, m), 1.43 (6 H, s), 1.28 (3 H, s), 1.24 (3 H, s), 1.10 (3 H, s), 1.05 (3 H, d); (c) (**7**) δ 4.84 (4 H, m), 4.55 (1 H, dd), 4.03 (1 H, d), 3.95 (1 H, m), 3.75 (1 H, m), 3.69 (2 H, m), 3.57 (2 H, m), 3.39 (3 H, s), 2.60 (1 H, dt), 2.17 (1 H, dd), 2.04 (1 H, m), 1.81 (3 H, d), 1.60–1.80 (3 H, m), 1.65 (3 H, s), 1.43 (3 H, s), 1.40 (3 H, s), 1.24 (3 H, s), 1.18 (3 H, s), 1.10 (3 H, s), 0.95 (9 H, s), 0.07 (3 H, s), 0.06 (3 H, s); (d) (**8**) δ 4.77 (1 H, d), 4.73 (2 H, dd), 4.52 (1 H, m), 4.21 (1 H, d), 3.89 (1 H, m), 3.72 (3 H, m), 3.56 (2 H, m), 3.39 (3 H, s), 2.97 (1 H, dd), 2.50–2.70 (2 H, m), 2.14 (1 H, dd), 2.06 (1 H, dd), 1.85–1.95 (2 H, m), 1.80 (3 H, d), 1.62 (3 H, s), 1.40 (6 H, s), 1.13 (3 H, s), 1.07 (3 H, s), 0.80 (3 H, d), 0.50 (9 H, s), 0.06 (6 H, s).

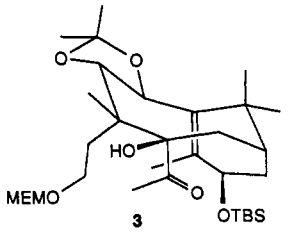
(10) (a) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731. (b) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455.

(11) It has recently been demonstrated that variety of Sm^{3+} species may be formed under different conditions. See, for example: (a) Evans, W. J.; Ulibarri, T. A. *J. Am. Chem. Soc.* **1987**, *109*, 4292. (b) Evans, W. J.; Grate, J. W.; Hughes, L. A.; Zhang, H.; Atwood, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 3278. (c) Evans, W. J.; Grate, J. W.; Bloom, I.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem.* Soc. **1985**, *107*, 405 and references contained therein.

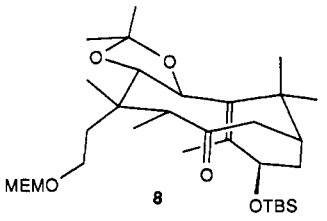
presence of Et_3N (4 equiv, 3 equiv of SmI_2, THF, 0 °C, 2 h), a 1:1 mixture of diols **9** was produced in high yield. Under these conditions, the Lewis acid mediated ring expansion process is completely shut down, and although the samarium ketyl is undoubtedly an intermediate in the formation of **9**, the fact that no loss of the tertiary hydroxyl is observed provides additional support for the conformation of **4** shown below.



On the other hand, the conformation (enforced by steric repulsion from the A ring) of **3** is one in which the hydroxyl–carbon bond is parallel to the p orbitals of the carbonyl group, and reduction is stereoelectronically more favorable than ring expansion. This is supported by the fact that **3** did not undergo ring expansion in the presence of Sm^{3+} (SmI_2, cyclohexene oxide, THF, 0 °C, 2 h), and, although some decomposition was observed, approximately 50% of **3** was recovered unchanged.



Apparently **7** cannot readily adopt a conformation that would facilitate ring contraction to provide **3**. However, there are conformations available to **7** that are stereoelectronically favorable for reduction to the samarium enolate, which must then be protonated to give **8**. That ketone **8** prefers the conformation shown below is supported by its UV absorption (λ_{max} 204 nm, ϵ 5736), a consequence of transannular conjugation of the double bond with the carbonyl group.[12] From this conformation, the samarium ketyl readily undergoes radical cyclization followed by further electron transfer and loss of OTBS to give **6**.



This process is novel in that it combines a Lewis acid promoted rearrangement with reductive loss of a hydroxyl substituent and ketyl cyclization. Efforts to address the generality of these findings are in progress.

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Registry No. **1**, 19605-80-2; **2**, 115941-39-4; **3**, 115913-10-5; **4**, 116003-21-5; **5**, 115913-11-6; **6**, 116865-11-3; **6** epoxidation derivative, 116865-15-7; **6** epoxidation-fragmentation derivative, 116865-16-8; **7**, 116865-12-4; **8**, 116865-13-5; **9** (isomer 1), 116865-14-6; **9** (isomer 2), 116947-12-7; SmI_2, 32248-43-4.

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(12) This is an interesting example of transannular olefin–ketone conjugation. This phenomenon, which is common to **8**, **2**, and several derivatives related to **2**,[7,10a] will be fully discussed in a forthcoming publication: Holton, R. A.; Williams, A. D.; manuscript in preparation. For related observations, see: (a) Huenig, S.; Martin, H. D.; Mayer, B.; Peters, K.; Prokschy, F.; Schmitt, M.; Von Schnering, H. G. *Chem. Ber.* **1987**, *120*, 195. (b) Beck, K.; Huenig, S.; Kleefeld, G.; Martin, H. D.; Peters, K.; Prokschy, F.; Von Schnering, H. G. *Chem. Ber.* **1986**, *119*, 543. (c) Klingensmith, K. A.; Puettman, W.; Vogel, E.; Michl, *J. Am. Chem. Soc.* **1983**, *105*, 3375 and references contained therein.

Highly Enantioselective Claisen-Type Acylation and Dieckmann Annulation

Summary: Enantioselective Claisen condensation reactions between various esters **1a–f** and 3-acyl-4(*S*)-IPTT **2a,b** employing lithium isopropylcyclohexylamide and HMPA gave acylated products **3a–j** in 29–77% yield and in 22–97% ee. Asymmetric Dieckmann-type annulation of **4a** with KH in DMF followed by methanolysis afforded bicyclic β-keto methyl ester **6a** in 69% overall yield and in 96% ee.

Sir: Carbon–carbon bond formation via Claisen and Dieckmann condensations is useful in the construction of functionalized synthons in the synthesis of biologically active natural products and drugs.[1,2] Here we report the first example of highly enantioselective Claisen-type acylations[3] and Dieckmann annulations utilizing 4(*S*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT][4] as chiral leaving group.

In both asymmetric reactions, the choice of the chiral leaving group seems to be crucial for high stereoselectivity. Thus, we designed asymmetric Claisen- and Dieckmann-type reactions based on thiazolidine-2-thione L*[4(*S*)-IPTT] (eq 1 and 2).[4]

The Claisen-type acylation was exploited for the construction of an asymmetric quarternary carbon atom which

(1) (a) Hauser, C. R.; Hudson, B. E., Jr. *Org. React. (N.Y.)* **1942**, *1*, 266 and references cited therein. (b) Schaefer, J. P.; Bloomfield, J. J. *Org. React. (N.Y.)* **1967**, *15*, 1 and references cited therein. (c) Walther, H.; Treibes, W.; Michaelis, K. *Chem. Ber.* **1956**, *89*, 60. (d) Johnson, D. H. *J. Chem. Soc.* **1958**, 1624. (e) Bloomfield, J. J.; Fennesy, P. V. *Tetrahedron Lett.* **1964**, *5*, 2273. (f) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; McGraw Hill: New York, 1968; pp 366–369. (g) Turecek, F.; Vystcil, A. *Collect. Czeckslov. Chem. Commun.* **1976**, *41*, 1571. (h) Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* **1981**, *22*, 1353. (i) Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883.

(2) Krauch, H.; Kunz, W. *Organic Name Reactions*; John Wiley & Sons, Inc.: New York, 1964; pp 94–96 and pp 124–125.

(3) For highly "diastereoselective" acylation employing a chiral auxiliary, see: (a) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron. Lett.* **1984**, *25*, 6015.

(4) (a) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (c) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289.

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