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Diastereoselective Additions of Chiral (*E*)-Crotylsilanes to in Situ Generated Oxonium Ions: A Direct Asymmetric Synthesis of Functionalized Homoallylic Ethers

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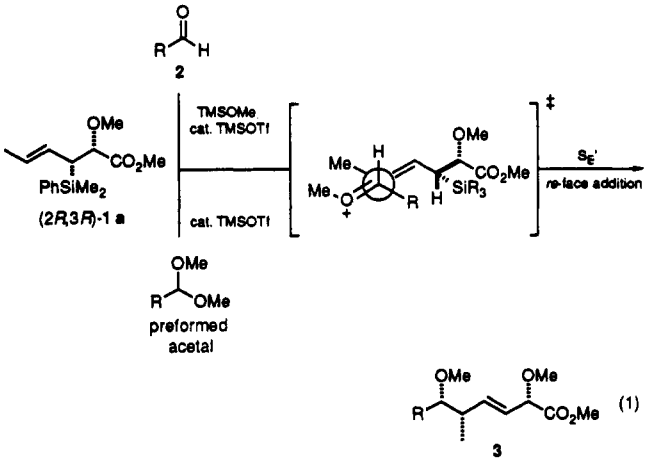
Received June 2, 1992

In recent reports from our laboratory, we have described the use of functionalized (*E*)-crotylsilanes as carbon nucleophiles in highly diastereo- and enantioselective addition reactions to preformed acetals and aldehydes. Those studies resulted in the development of a useful strategy for the asymmetric construction of homoallylic ethers,[1] tetrahydrofurans,[2] and γ-alkoxy-α-amino acid synthons,[3] subunits of many polyketide, and amino acid derived natural products. In experiments designed to optimize these reaction conditions, we have determined that the enantioselective condensation reactions can be performed by using a documented procedure for the in situ generation of an oxonium ion.[4] The action of a Lewis acid, (trimethylsilyl)trifluoromethanesulfonate (TMSOTf) and a silyl ether (Me_3SiOR) reagent cleanly promotes the asymmetric addition from the corresponding aldehyde (eq 1).[4d,e]



This note describes the results of our experiments concerning the asymmetric synthesis of homoallylic ethers employing the illustrated chiral (*E*)-crotylsilanes with the in situ generation of an oxonium ion from an achiral aldehyde. Thus, combining the chiral (*E*)-crotylsilane reagent **1** with an aldehyde **2** and the trimethylsilyl ether, TMSOMe[5] or TMSOBn,[5] followed by the Lewis acid, TMSOTf produced the homoallylic ether **3**. In most cases excellent levels of disastereo- and enantioselection were achieved, presumably through the oxonium ion species illustrated in the eq 1.

Key features of this process include the fact that highly functionalized homoallylic ethers are constructed in a three-component, one-pot operation with generally useful levels of stereoselection. Operationally, the reaction is simplified by removing the requirement for a preformed acetal.[6] In this regard, for the cases employing trimethylsilyl benzyl ether as the alkoxy exchange reagent, a benzyl moiety is installed on the secondary homoallylic ether without loss of diastereoselection (entries 3–9, Table I). The potential utility of such transformations is rather obvious, in the context of organic synthesis a protection step is removed from a reaction sequence. With regard to acyclic diastereoselective reaction processes the present study demonstrates that our developing chiral allylsilane bond construction methodology can be extended to include the in situ generation and capture of an oxonium ion.[4]

A summary of Lewis acid catalyzed addition reactions of **1a–d** to aldehydes **2a–i** is given in Table I. The diastereomerically pure *syn*- and *anti*-(*E*)-crotylsilanes employed in this study were prepared as previously reported.[7,8] For all the cases examined, the product homoallylic ethers **3** were obtained by mixing equimolar quantities of the silane reagent **1**, aldehyde **2**, and the trimethylsilyl ether at −78 °C followed by the addition of 0.2–1.0 equiv of TMSOTf. The resulting reaction mixture was then warmed to the indicated temperature (Table I) for 8–24 h with stirring to afford, after extractive isolation, **3a–i** in good to excellent yield. The reactions generally proceed with high levels of diastereoselection for the formation of the syn-C5,C6 isomer and are consistent with an anti-$S_{E'}$ mechanism as previously reported for intermolecular additions of chiral allylsilanes (entries 3–9).[9] The aliphatic and branched aldehydes (entries 1–6) were less reactive than the aromatic aldehydes (entries 7–9) and generally required higher temperatures and longer reaction times to ensure efficient conversion. The reactions of the aliphatic aldehydes, acetaldehyde, and valeraldehyde were nonselective (entries 1 and 2).

Stereochemical Assignment. Assignment of stereochemistry for the major C5,C6-syn isomer is based on comparison of the vicinal coupling constants between the C5/C6 stereogenic centers. In four cases, authentic sam-

† Recipient of a Graduate Fellowship of the Organic Chemistry Division from the American Chemical Society 1992–1993, sponsored by Pfizer Inc.

(1) (a) Aryl acetals: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (b) Heterosubstituted acetals: Panek, J. S.; Yang, M. *J. Org. Chem.* **1991**, *56*, 5755–5758.

(2) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868–9870.

(3) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063–4064.

(4) (a) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808–2809. (b) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765–766. (c) Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121–1124. For the use of TMSOTf see: (d) Intermolecular addition: Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779–4782. (e) Intramolecular Addition: Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211–2213.

(5) Coles, B. F.; Walton, D. R. M. *Synthesis* **1975**, 390–391.

(6) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899–3910. (c) Acid-catalyzed acetalization [*p*-TsOH/BnOH/Ph/heat/Dean–Stark trap] resulted in low chemical yields (<20% after purification).

(7) For chiral (*E*)-vinylsilanes in the Ireland–Claisen rearrangement, see: (a) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431–3438. For chiral (*Z*)-vinylsilanes in the Ireland–Claisen rearrangement, see: (b) Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323–4326.

(8) Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344.

(9) The antiperiplanar transition state for intermolecular chiral allysilane additions was originally proposed by Kumada and co-workers: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. For Lewis acid catalyzed intramolecular additions of certain allylsilanes and -stannanes to aldehydes, a synclinal arrangement of the reacting olefins has been postulated (cf.: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655–1660). (b) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865–2868. For diastereoselective $S_{E'}$ additions of optically active allenylstannanes, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 3211–3213.

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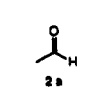
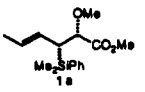
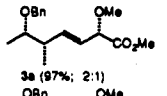
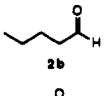
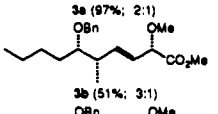
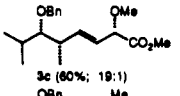
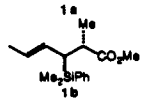
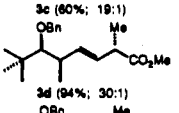
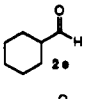
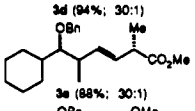
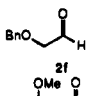
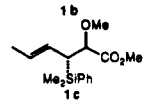
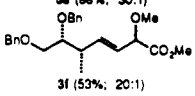
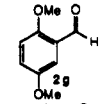
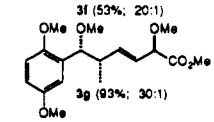
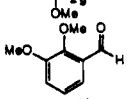
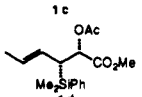
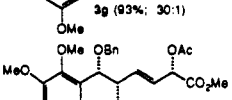
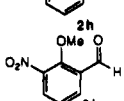
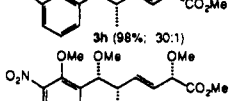
Table I. Enantioselective Additions of (*E*)-Crotylsilanes to Aldehydes

entry	aldehydes	(*E*)-crotylsilane[a]	reaction cond[b] (equiv of TMSOTf)	major diastereomer[c] (%;[d] 5,6 syn/anti ratio[e])
1	 2a	 1a	TMSOBn/-78°C/15h (1.0 equiv)	 3a (97%; 2:1)
2	 2b	1a	TMSOBn/-50°C/24h (1.0 equiv)	 3b (51%; 3:1)
3	 2c	1a	TMSOBn/-50°C/24h (1.0 equiv)	 3c (60%; 19:1)
4	 2d	 1b	TMSOBn/-50°C/20h (1.0 equiv)	 3d (94%; 30:1)
5	 2e	1b	TMSOBn/-50°C/16h (1.0 equiv)	 3e (88%; 30:1)
6	 2f	 1c	TMSOBn/-50°C/24h (1.0 equiv)	 3f (53%; 20:1)
7	 2g	1c	TMSOBn/-78°C/16h (0.2 equiv)	 3g (93%; 30:1)
8	 2h	 1d	TMSOBn/-78°C/10h (0.2 equiv)	 3h (98%; 30:1)
9	 2i	1a	TMSOBn/-78°C/18h (1.0 equiv)	 3i (92%; 30:1)

[a] The (*E*)-crotylsilanes were obtained from a Claisen rearrangement on the (*E*)- or (*Z*)-vinylsilane, see ref 7 and for 2,3-*anti*-α-methyl-β-silylhexenoate see ref 8. [b] All reactions were initiated at −78 °C in CH_2Cl_2 at 0.2–0.25 M in substrate using 1.2 equiv of aldehydes. [c] The absolute stereochemistry of the major diastereomer was assigned based on an anti addition [S_E' mechanism] of the (*E*)-crotylsilanes to the C=X π-bond; cf. refs 1 and 9. [d] All yields are based on pure materials isolated by chromatography on SiO_2. [e] Ratio of products was determined by ^1H NMR (400 MHz), operating at S/N ratio of >200:1.

ples **3f–i** were available for direct comparison from our earlier studies concerning the asymmetric additions to the preformed acetals.

In conclusion, we have shown that the asymmetric additions of optically active (*E*)-crotylsilanes to oxonium ions generated in situ from the corresponding aldehydes expands the scope and utility of our developing chiral allylsilane bond construction methodology. These reactions are currently under further investigation so as to more clearly define the factors influencing reactivity and selectivity of these chiral organosilane reagents.

Experimental Section[10]

Representative Experimental Procedure for Diastereoselective Additions of Chiral (*E*)-Crotylsilanes to in Situ Generated Oxonium Ions. (*E*)-(2*S*,5*S*,6*R*)-Methyl 6-(2,5-Dimethoxy-3-nitrophenyl)-2,6-dimethoxy-5-methylhex-3-enoate (3i). A solution of 2,5-dimethoxy-3-nitrobenzaldehyde (41.9 mg, 0.2 mmol), trimethylsilyl ether[5] (TMSOMe; 24 mg, 0.24 mmol), and (2*R*,3*R*)-methyl α-methoxy-β-(dimethylphenylsilyl)-(*E*)-hex-4-enoate (**1a**; 56 mg, 0.19 mmol) in 1.5 mL of dry CH_2Cl_2 (0.13 M) was cooled to −78 °C and treated with (trimethylsilyl)trifluoromethanesulfonate (TMSOTf; 36 μL, 0.19 mmol). The reaction mixture was stirred at −78 °C for 18 h before being diluted with a solution of $NaHCO_3$. This mixture was stirred for 2 min before extraction with Et_2O (2 × 5 mL). The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give crude **3i**. The crude oil was flash chromatographed[11] on silica gel (15% EtOAc–petroleum ether eluant) to afford 65 mg (theoretical 71 mg, 92% yield) of pure **3i**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1 H, *J* = 3.2 Hz), 7.11 (d, 1 H, *J* = 3.2 Hz), 5.79–5.73 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.36–5.29 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.39 (d, 1 H, *J* = 6.8 Hz), 4.10 (d, 1 H, *J* = 7.2 Hz), 3.81 (s, 6 H), 3.66 (s, 3 H), 3.29 (s, 3 H), 3.22 (s, 3 H), 2.52–2.50 (m, 1 H), 1.05 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 155.2, 145.5, 143.6, 138.2, 137.6, 125.2, 118.6, 109.1, 81.0, 80.5, 62.7, 57.4, 57.1, 56.0, 52.1, 43.0, 15.5; IR (neat) ν_{max} 2950, 1780, 1500, 1450, 1350, 1300, 850 cm^{-1}; CIMS (NH_3 gas) 784, 626, 594, 401, 352, 320, 226, 138; CIHRMS M^+ (calculated for $C_{18}H_{25}O_8N$) 401.1924, (found) 401.1955; $[\alpha]^{23}_D$ = +98° (*c* 0.7, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*S*)-Methyl 6-(benzyloxy)-2-methoxy-4-methylhept-3-enoate (3a): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.26 (m, 5 H), 5.89 (dd, 1 H, *J* = 7.6, 15.8 Hz), 5.46 (dd, 1 H, *J* = 7.6, 15.6 Hz), 4.54 and 4.43 (AB q, 2 H, J_{AB} = 11.6 Hz), 4.20 (d, 1 H, *J* = 7.2 Hz), 3.73 (s, 3 H), 3.39–3.35 (m, 1 H), 3.34 (s, 3 H), 2.42–2.35 (m, 1 H), 1.09 (d, 3 H, *J* = 6.0 Hz), 1.03 (d, 3 H, *J* = 6.8 Hz); IR (neat) ν_{max} 3100–2800, 1750, 1500, 1450, 1370, 1360, 1200, 950, 850 cm^{-1}; CIMS (NH_3 gas) 310, 275, 217, 185, 125,

(10) Infrared spectra were recorded on a Perkin-Elmer 1310-infrared spectrophotometer. ^1H NMR spectra were recorded at 400 MHz (93.94 kG) at ambient temperature. ^{13}C NMR were recorded at 100 MHz or at 67 MHz at ambient temperature in $CDCl_3$. All ^{13}C spectra were recorded with complete proton decoupling. High-resolution and low-resolution mass spectra were obtained on a Finnegan MAT-90 spectrometer in the Boston University Mass Spectrometry Laboratory. Analytical thin-layer chromatography was performed on Whatman Reagent 0.25-mm silica gel 60-A plates. Flash chromatography was performed as previously described.[11] Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All extraction and chromatographic solvents, ethyl acetate (EtOAc), ethyl ether (Et_2O), and petroleum ether were distilled prior to use. All reactions were run in oven-dried glassware, sealed with a rubber septum, and stirred with a magnetic stirring bar under an atmosphere of N_2. Unless otherwise noted, commercial reagents were purchased and used without prior purification.

(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

105, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{17}H_{28}NO_4$) 310.2018, (found) 310.2010; $[\alpha]^{23}_D$ = +34.4° (c 0.75, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*S*)-Methyl 6-(benzyloxy)-2-methoxy-4-methyldec-3-enoate (3b): ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5 H), 5.93 (dd, 1 H, *J* = 7.2, 15.6 Hz), 5.47 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.53 and 4.49 (AB q, 2 H, J_{AB} = 11.5 Hz), 4.21 (d, 1 H, *J* = 7.6 Hz), 3.74 (s, 3 H), 3.36 (s, 3 H), 3.28–3.25 (m, 1 H), 2.54–2.52 (m, 1 H), 1.60–1.25 (m, 6 H), 1.05 (d, 3 H, *J* = 3.2 Hz), 0.87 (t, 3 H, *J* = 6.8 Hz); IR (neat) ν_{max} 3000–2800, 1750, 1500, 1480, 1370, 1350, 1100 cm^{-1}; CIMS (NH_3 gas) 352, 335, 303, 247, 227, 195, 157, 127, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{20}H_{34}NO_4$) 352.2488, (found) 352.2491; $[\alpha]^{23}_D$ = +21.6° (c 0.5, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*S*)-Methyl 6-(benzyloxy)-6-isopropyl-2-methoxy-4-methylhex-3-enoate (3c): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.23 (m, 5 H), 5.83 (dd, 1 H, *J* = 8, 15.6 Hz), 5.41 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.46 and 4.43 (AB q, 2 H, J_{AB} = 11.2 Hz), 4.12 (d, 1 H, *J* = 7.2 Hz), 3.63 (s, 3 H), 3.27 (s, 3 H), 2.91 (t, 1 H, *J* = 5.6 Hz), 2.42–2.39 (m, 1 H), 1.76–1.71 (m, 1 H), 0.99 (d, 3 H, *J* = 6.4 Hz), 0.85 (d, 6 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.4, 138.9, 128.27, 127.4, 123.7, 88.5, 81.4, 75.1, 57.1, 52.1, 39.7, 37.3, 31.1, 20.3, 17.7, 15.2; IR (neat) ν_{max} 2900, 1750, 1500, 1450, 1370, 1350, 1200, 1100 cm^{-1}; CIMS (NH_3 gas) 338, 321, 289, 247, 217, 213, 181, 163, 127, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{19}H_{32}NO_4$) 338.2337, (found) 338.2331; $[\alpha]^{23}_D$ = +76° (c 0.25, CH_2Cl_2).

(*E*)-(2*S*,5*R*,6*S*)-Methyl 6-(benzyloxy)-2,5,7,7-tetramethyloct-3-enoate (3d): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (m, 5 H), 5.52 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.36 (dd, 1 H, *J* = 7.6, 15.6 Hz), 4.51 and 4.49 (AB q, 2 H, J_{AB} = 11.6 Hz), 3.55 (s, 3 H), 3.03–2.99 (m, 1 H), 2.88 (d, 1 H, *J* = 3.6 Hz), 2.45–2.43 (m, 1 H), 1.15 (d, 3 H, *J* = 7.2 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 0.86 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 139.3, 138.9, 128.2, 127.4, 127.2, 126.6, 90.4, 74.9, 51.7, 42.8, 38.1, 37.0, 27.2, 17.3, 15.9; IR (neat) ν_{max} 3100–2800, 1740, 1450, 1380, 1200, 1100, 950, 750, 700 cm^{-1}; CIMS (NH_3 gas) 336, 276, 261, 211, 199, 155, 141, 91, 85, 73, 57; CIHRMS M + NH_4^+ (calculated for $C_{20}H_{34}NO_3$) 336.2537, (found) 336.2538; $[\alpha]^{23}_D$ = +28.1° (c 1.1, CH_2Cl_2).

(*E*)-(2*S*,5*R*,6*S*)-Methyl 6-(benzyloxy)-6-cyclohexyl-2,5-dimethylhex-3-enoate (3e): ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5 H), 5.58–5.51 (m, 2 H), 4.55 and 4.49 (AB q, 2 H, J_{AB} = 11.2 Hz), 3.64 (s, 3 H), 3.14–3.10 (m, 1 H), 2.99 (t, 1 H, *J* = 5.6 Hz), 2.48–2.45 (m, 1 H), 1.92–1.61 (m, 7 H), 1.24 (d, 3 H, *J* = 6.8 Hz), 1.22–1.09 (m, 4 H), 1.05 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 139.1, 136.08, 128.3, 127.9, 127.5, 127.3, 88.2, 75.1, 57.1, 51.7, 42.8, 41.1, 39.1, 30.6, 28.3, 26.6, 26.6, 17.4, 15.1; IR (neat) ν_{max} 3100–2750, 1780, 1450, 1280, 1200, 1100, 950, 750, 700 cm^{-1}; CIMS (NH_3 gas) 237, 205, 149, 141, 91, 85; CIHRMS M + NH_4^+ (calculated for $C_{22}H_{36}NO_3$) 362.2695, (found) 362.2697; $[\alpha]^{23}_D$ = +32.9° (c 0.75, CH_2Cl_2).

(*E*)-(2*R*,5*S*,6*R*)-Methyl 6,7-bis(benzyloxy)-2-methoxy-5-methylhept-3-enoate (3f): ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.16 (m, 10 H), 5.84–5.76 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.44–5.38 (dd, 1 H, *J* = 7.2, 15.6 Hz), 4.61 and 4.46 (AB q, 2 H, J_{AB} = 11.6 Hz), 4.43 and 4.40 (Ab q, 2 H, J_{AB} = 12.0 Hz), 4.09 (d, 1 H, *J* = 7.2 Hz), 3.62 (s, 3 H), 3.58–3.39 (m, 3 H), 3.23 (s, 3 H), 2.49–2.48 (m, 1 H), 0.97 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 139.1, 138.8, 138.3, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.6, 127.5, 124.5, 81.5, 81.4, 77.2, 73.4, 72.7, 71.2, 57.0, 52.2, 38.6, 15.2; IR (neat) ν_{max} 3100, 2200, 1725, 1635, 1450, 1200, 1100 cm^{-1}; CIMS (NH_3 gas) 416, 226, 189, 181, 145, 104, 91, 75; CIHRMS M + NH_4^+ (calculated for $C_{24}H_{34}NO_5$) 416.5377, (found) 416.53774; $[\alpha]^{23}_D$ = +32.97° (c 0.56, CH_2Cl_2).

(*E*)-(2*R*,5*S*,6*R*)-Methyl 6-(2,5-dimethoxyphenyl)-2,6-dimethoxy-5-methylhex-3-enoate (3g): ^1H NMR (400 MHz, $CDCl_3$) δ 6.88–6.87 (m, 1 H), 6.75–6.74 (m, 2 H), 5.89–5.83 (dd, 1 H, *J* = 7.6, 15.2 Hz), 5.38–5.33 (dd, 1 H, *J* = 7.6, 15.6 Hz), 4.49 (d, 1 H, *J* = 6.0 Hz), 4.13 (d, 1 H, *J* = 7.6 Hz), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.22 (s, 3 H), 3.20 (s, 3 H), 2.55 (m, 1 H), 1.02 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 153.6, 151.5, 139.6, 129.8, 123.9, 113.0, 112.6, 111.2, 81.3, 80.4, 57.1, 56.5, 55.7, 55.6, 51.9, 42.2, 14.9; IR (neat) ν_{max} 2995, 1750, 1490, 1475, 1275, 1210, 1100, 1050; CIMS (NH_3 gas) 338, 275, 243, 215, 181, 151, 95, 75, 45; CIHRMS M + NH_4^+ (calculated for $C_{18}H_{30}NO_6$) 356.2073, (found) 356.2071; $[\alpha]^{23}_D$ = +17.24° (c 1.0, CH_2Cl_2).

(*E*)-(2*S*,5*S*,6*R*)-Methyl 6-(benzyloxy)-6-(2,3-dimethoxyphenyl)-2-acetoxy-5-methylhex-3-enoate (3h): ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5 H), 7.06 (t, 1 H, *J* = 8.0 Hz), 6.98 (d, 1 H, *J* = 6.4 Hz), 6.83 (d, 1 H, *J* = 6.8 Hz), 5.87 (dd, 1 H, *J* = 7.6, 15.6 Hz), 5.43 (dd, 1 H, *J* = 7.2, 15.6 Hz), 5.29 (d, 1 H, *J* = 7.6 Hz), 4.66 (d, 1 H, *J* = 6.8 Hz), 4.42 and 4.24 (AB q, 2 H, J_{AB} = 12 Hz), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.65 (s, 3 H), 2.65–2.63 (m, 1 H), 2.04 (s, 3 H), 1.09 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (67 MHz, $CDCl_3$) δ 170.1, 169.3, 152.3, 147.3, 139.9, 138.6, 133.9, 128.2, 127.6, 127.4, 123.8, 121.7, 119.6, 111.2, 78.2, 73.2, 70.7, 60.5, 55.6, 52.3, 42.6, 20.6, 15.1; IR (neat) ν_{max} 3050, 2950, 1730, 1600, 1490, 1430, 1280, 1230 cm^{-1}; CIHRMS M + NH_4^+ (calculated for $C_{25}H_{34}NO_7$) 460.2335, (found) 460.2348; $[\alpha]^{23}_D$ = +58.2° (c 1.5, CH_2Cl_2).

Acknowledgment. This work has been financially supported by the National Institutes of Health (CA472249). We are grateful to Mr. Michael Creech for performing mass spectral measurements.

Supplementary Material Available: NMR spectra for all reaction products (16 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.

Studies on the Synthesis of Pentacyclic *Strychnos* Indole Alkaloids. Closure of E Ring by Pummerer Cyclization

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Received May 19, 1992

The development of new, general synthetic routes to pentacyclic *Strychnos* indole alkaloids[1] based on the closure of the five-membered E ring, by formation of the crucial quaternary C-7[2] center in the last synthetic steps from appropriate hexahydro-1,5-methanoazocino[4,3-*b*]-indole systems, has received attention during the last years.[3,4] Cyclization of a thionium ion, such as **1a**, generated by treatment of *amino* dithioacetal **2a** with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) was successful when R = H.[3] Following this procedure we have reported the total synthesis of the *Strychnos* alkaloids (±)-tubifoline, (±)-tubifolidine, (±)-19,20-dihydroakuammicine,[3] and (±)-tubotaiwine.[5] Similar cyclizations from thionium salts **1b**, generated either from *amido* dithioacetal **2b** (R = H) or by Pummerer rearrangement from *amido* sulfoxides **3b** (R = H, CO_2Me, *p*-$MeC_6H_4SO_2$, or *p*-$MeOC_6H_4SO_2$) resulted in failure.[3,4] Both our studies and those reported by Magnus have demonstrated that a limiting structural factor in the above cyclizations is the presence of an amide carbonyl group, either exocyclic or endocyclic with respect to the piperidine ring, since all

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0022-3263/92/1957-5792$03.00/0 © 1992 American Chemical Society