Use of β-Silylethyl Vinyl Ketone as a β-Hydroxyethyl Vinyl Ketone Synthon in the Robinson Annulation Reaction

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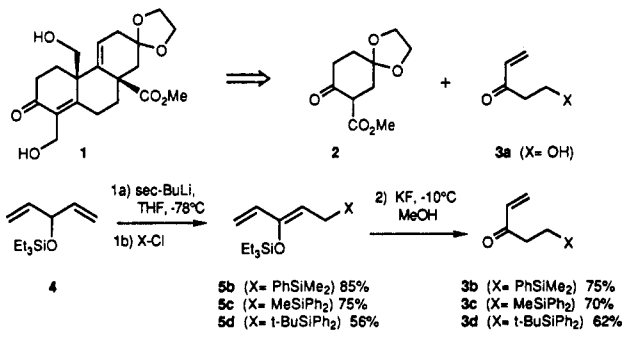
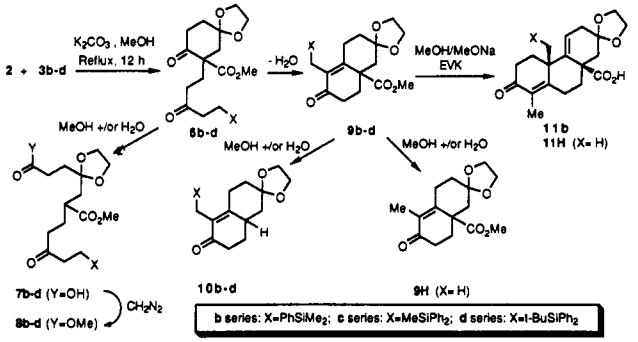
Received July 27, 1992

In conjunction with our interest in highly oxygenated terpenoids, we wished to effect the synthesis of tricyclic diol **1**. While standard synthetic analysis would suggest the union of β-keto ester **2** with 2 equiv of β-hydroxyethyl vinyl ketone **3a**, it is clear that the labile nature of such aldol derivatives preclude their use under the conditions of the Robinson annulation reaction.[1] Since the Kumada–Fleming–Tamao oxidation provides an excellent means of silane to alcohol conversion,[2] our initial studies involved investigation of the annulation chemistry of β-silylethyl vinyl ketone derivatives **3b–d**. Synthesis of the requisite enone reagents is readily accomplished by the method of Oppolzer et al., who had previously prepared the parent (trimethylsilyl)- and (triethylsilyl)ethyl enones **3** (X = TMS, TES), but did not report any attempts at annulation chemistry with these derivatives.[3,4]



Reaction of **2**[5] and **3b** in the presence of potassium carbonate in methanol at reflux for 12 h provided bicyclic enone **9b** in 59% yield accompanied by traces of protiodesilylation product **9H** and deacylation[6] product **10b**. Treatment of the polar reaction residues (presumably primarily acid **7b**) with diazomethane provided an additional 25% yield of retro-Claisen product **8b**.[7,8] Unfortunately, submission of **9b** to sodium methoxide in methanol at reflux in the presence of ethyl vinyl ketone (EVK), did not give any of the desired tricyclic derivative **11b**, but exclusively yielded **11H**. Control studies reveal that **11H** arose through the intermediacy of **9H**, protiodesilylation being faster than the second annulation reaction. Other conditions lead to either no reaction (DBU or potassium *tert*-butoxide/2-methyl-2-propanol/THF reflux) or provide none of the desired silyl compound **11b**.

Since desilylation of intermediate **9** is presumably a consequence of alkoxide (and or water) attack at the silicon atom, reagents **3c–d** were also tested in the annulation reaction. As can be seen from the table below, this modification has conferred greater stability characteristics upon the silyl moiety; unfortunately, this comes at the expense of the intramolecular aldol–dehydration step which has slowed to the point where deacylation and retro-Claisen reactions have become the dominant processes.



SM	Yield 8	Yield 9	Yield 9H	Yield 10
3b	25 %	59%	trace	trace
3c	30 %	41%	5 %	5 %
3d	60 %	trace	trace	22 %

Reaction of compound **9b** with BF_3·2AcOH complex[2] in $CDCl_3$ was followed by ^1H NMR which showed slow collapse of the aromatic protons into a singlet indicating formation of benzene. No signals could be detected from products arising from protiodesilylation of the allylsilane moiety; although simple allylsilanes are normally more reactive than arylsilanes,[9,10] the allylsilane present in **9b** is expectedly deactivated by the carbonyl moiety. Fluorsilane **12b** was not the only product detected in the crude mixture as indicated by two singlets around 3.7 ppm accounting for two methyl ester-containing species, as well as two doublets (ca. 0.4 ppm) corresponding to the dimethylsilanes. The second product (about 25–30% of the material) is free ketone **13b**, arising from competitive deketalization of **12b**. This crude mixture was submitted to oxidation of the carbon–silicon bond by addition of sodium carbonate and peracetic acid, thereby providing the desired alcohol **14** in 64% isolated yield.

Enone **9b** can be converted to the saturated intermediate **15b** in 95% yield via treatment with 3 equiv of lithium in ammonia–THF[11] at −78 °C for 1 h, followed by quenching the excess lithium at −78 °C with isoprene. Further pro-

(1) For a discussion of this problem see: Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1983**, *24*, 3311 and references cited therein.

(2) (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (b) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (c) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. (d) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. (e) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, J. *J. Chem. Soc., Chem. Commun.* **1985**, 318. (f) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229. (g) Tamao, K. J. *Synth. Org. Chem., Jpn.* **1988**, *46*, 861. (h) Kolb, H. C.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 6187. (i) Overmann, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647. (j) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (k) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M. *J. Org. Chem.* **1992**, *57*, 1571. For a recent review, see: Fleming, I. *Pure Appl. Chem.* **1988**, *60*, 71.

(3) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002.

(4) For an alternative large-scale synthesis of reagent **3b**, see: Emeric, G. Ph.D. Thesis, Purdue University, 1991.

(5) Pariza, R. J.; Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1983**, *13*, 243. Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2306.

(6) Greene, A. E.; Cruz, A.; Crabbe, P. *Tetrahedron Lett.* **1976**, *76*, 2707. Parish, E. J.; Huang, B.-S.; Miles, D. H. *Synth. Commun.* **1975**, *5*, 341.

(7) Use of sodium carbonate (rate a factor of 2 slower) or cesium carbonate (rate a factor of 2 faster) did not improve the yield or eliminate the retro-Claisen product.

(8) Attempts to trap the water produced in the formation of enone **9** by adding molecular sieves or magnesium sulfate (either directly to the reaction mixture or in a soxhlet extractor) failed to prevent the formation of carboxylic acid **7**. Use of more hindered alcohols like 2-propanol as reaction solvent also fail to prevent the retro-Claisen reaction.

(9) Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745. Magar, S. S.; Desai, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360.

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(11) Caine, D. *Organic Reactions*; John Wiley: New York, 1976; Vol. 23, Chapter 1, pp 1–258.

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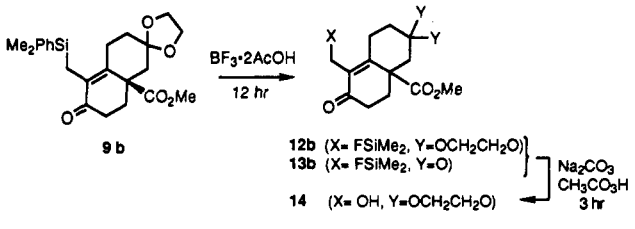
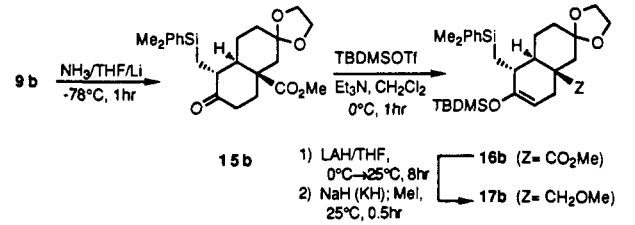


cessing of **15b** to silyl enol ether **16b** (90%) followed by LAH reduction and direct methylation with potassium hydride doped sodium hydride[12] provides **17b** (47% overall), a compound having its four "oxygenated" carbons suitably differentiated for subsequent synthetic manipulations.



Experimental Section

General. All reactions were performed under a positive pressure of argon in glassware which was washed with dilute aqueous sodium hydroxide prior to flame drying and which were equipped with rubber septa for the introduction of reagents via syringe. THF was purified by distillation from benzophenone–sodium ketyl under argon. All compounds reported have been analyzed by exact mass and appear to be homogeneous by ^{1}H NMR and ^{13}C NMR. Proton NMR spectra were recorded on a General Electric QE-300 (300 MHz) and a Varian Gemini-200 (200 MHz) spectrometer. J values are given in Hz. Carbon NMR spectra were recorded on a General Electric QE-300 (75 MHz) or a Varian Gemini 200 (50 MHz). Compounds of >95% purity were characterized on a Finnigan 4000 mass spectrometer and a CEC 21 110 B high-resolution mass spectrometer with use of electron impact and chemical ionization, with molecular ion designated as M. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer. All silyl chlorides were purchased from Aldrich.

5-(Dimethylphenylsilyl)-1-penten-3-one (3b). KF (Aldrich, 34.88 mg, 0.6 mmol) was added portionwise to a stirred solution of **5b** (100 mg, 0.3 mmol) in methanol (5 mL) at −5 °C under Ar. The resulting solution was allowed to react for 3 h at 10 °C. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution and then dried over anhydrous Na_2SO_4. The solvent was evaporated to give an oil, which was subjected to column chromatography on silica gel using 5% EtOAc in hexane as eluent to afford 49.1 mg (75%) of **3b**: IR (CCl_4) 1680, 1618 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.50 (2 H, m), 7.39–7.34 (3 H, m), 6.34 (1 H, ABX, J = 18.5, 10.4, dd), 6.19 (1 H, ABX, J = 18.5, 0.8, dd), 5.75 (1 H, ABX, J = 10.4, 0.8, dd), 2.55 (2 H, m), 1.07 (2 H, m), 0.31 (6 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.50 (e), 138.42 (e), 136.07 (o), 133.63 (o), 129.16 (o), 127.94 (o), 127.77 (e), 34.11 (e), 9.14 (e), −3.48 (o); MS (EI) m/z 218, 203, 135, 55; exact mass for $C_{13}H_{18}OSi$ (M) found 218.1108 (calcd 218.1127).

(*Z*)-5-(Dimethylphenylsilyl)-3-[(triethylsilyl)oxy]-1,3-pentadiene (5b). A 1.22 M solution of *s*-BuLi (0.93 mL, 1.14 mmol) in cyclohexane was added dropwise to a stirred 1.5 M solution of triethylsilyl ether **4** (206 mg, 1.04 mmol) in dry THF at −78 °C under Ar. After 30 min at −78 °C, chlorodimethylphenylsilane (0.18 mL, 1.16 mmol) was added slowly to the deep orange solution. After 10 min at −78 °C, the decolorized mixture was poured into saturated aqueous NH_4Cl solution. The organic layer was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4 and evaporated in vacuo to leave a residue, which was chromatographed on silica gel, using hexane as eluent to afford 307 mg (85%) of **5b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56–7.34 (5 H, m), 6.18–6.09 (1 H, J = 17, 11, dd), 5.20 (1 H, J = 17, d), 4.88 (1 H, J = 11.8, d), 4.79 (1 H, t), 1.77 (2 H, J = 8.4, d), 1.04–0.95 (9 H, br t), 0.77–0.65 (6 H, br q), 0.29 (6 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.25 (e), 139.59 (e), 136.42 (o), 134.09 (o), 129.48 (o), 128.29 (o), 111.76 (o), 110.44 (e), 78.04 (e), 77.41 (e), 76.77 (e), 15.86 (e), 7.05 (o), 5.85 (e), −2.93 (o); MS (EI) m/z 332, 135; exact mass for $C_{19}H_{32}OSi_2$ (M) found 332.1989 (calcd 332.1992).

2,3,4,4a,5,6,7,8-Octahydro-1-[(dimethylphenylsilyl)-methyl]-4a-[(methyloxy)carbonyl]-6,6-(ethylenedioxy)-2-(1*H*)-naphthalenone (9b). To β-keto ester **2** (370 mg, 1.73 mmol) and K_2CO_3 (478 mg, 3.46 mmol) in methanol (20 mL) at reflux was slowly added enone **3b** (565 mg, 2.6 mmol) diluted in methanol (5 mL). The mixture was gently heated at reflux for 12 h. The resulting solution was cooled to room temperature, and the solvent was removed in vacuo. The oil was taken up in EtOAc (30 mL) and water (20 mL). The organic layer was separated and the solvent evaporated. The crude oil was purified by column chromatography (20% EtOAc in hexane) yielding the desired product **9b** (420 mg, 59%), along with a trace amount of **9H** and **10b**. The aqueous layer was acidified with 5% HCl to pH 3, extracted with EtOAc, and evaporated to give a pale yellow oil. The residue was methylated with excess diazomethane (prepared from diazald) and then purified by column chromatography (20% EtOAc in hexane) to afford 200 mg of retro-Claisen product **8b** (25%). **9b**: IR (CCl_4) 1724, 1664, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.45 (2 H, m), 7.31–7.29 (3 H, m), 3.98–3.78 (4 H, m), 3.66 (3 H, s), 2.45 (1 H, m), 2.09 (2 H, s), 1.33 (1 H, m), 1.22–2.66 (8 H, m), 0.26 (3 H, s), 0.20 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.54 (e), 174.86 (e), 149.49 (e), 138.94 (e), 134.43 (e), 133.72 (o), 129.05 (o), 127.69 (o), 106.80 (o), 64.38 (e), 64.01 (e), 52.14 (o), 48.96 (e), 44.11 (e), 35.10 (e), 34.29 (e), 33.95 (e), 27.56 (e), 15.29 (e), −2.75 (o), −2.87 (o); MS (EI) m/z 414, 399, 355, 135; exact mass for $C_{23}H_{30}O_5Si$ (M) found 414.1863 (calcd 414.1863). **8b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5–7.32 (5 H, m), 3.86 (4 H, s), 3.64 (3 H, s), 3.62 (3 H, s), 2.36–1.67 (13 H, remaining protons, m), 0.94 (2 H, m), 0.25 (6 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.05 (e), 176.78 (e), 174.47 (e), 138.84 (e), 134.09 (o), 129.59 (o), 128.38 (o), 110.18 (e), 65.43 (e), 65.35 (e), 51.90 (o), 51.82 (o), 40.34 (o), 39.92 (e), 39.47 (e), 37.54 (e), 32.64 (e), 28.92 (e), 27.35 (e), 9.41 (e), −3.08 (o); MS (CI) m/z 465 (M + 1), 433, 387, 325, 281, 175, 159; exact mass for $C_{24}H_{36}O_7Si$ (M + 1) found 465.2299 (calcd 465.2309).

2,3,4,4a,5,6,7,8-Octahydro-1-(hydroxymethyl)-4a-[(methyloxy)carbonyl]-6,6-(ethylenedioxy)-2(1*H*)-naphthalenone (14). To enone **9b** (70 mg, 0.17 mmol) in $CDCl_3$ (10 mL) was slowly added BF_3·2HOAc complex (Fluka, 63 mg, 0.33 mmol). The reaction was followed by ^{1}H NMR. After 10 min, the reaction was 40% complete, after 1 h, 87%. After 12 h, Na_2CO_3 (excess) was added to the solution followed by peracetic acid (FMC, 35% solution, 70 μL, 0.26 mmol). Column chromatography allowed the isolation of the desired β-keto alcohol **14** (35 mg, 64%): IR (CCl_4) 3024 (broad, OH), 1728, 1662, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (2 H, s), 4.04–3.75 (4 H, m), 3.73 (3 H, s), 3.06–2.99 (1 H, m), 2.7 (2 H, J = 5.7, 16.5, dt), 2.6 (1 H, J = 3, 13.8, dd), 2.46–2.19 (3 H, m), 1.99–1.74 (3 H, m), 1.60 (1 H, J = 13, br d); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.51 (e), 174.31 (e), 157.38 (e), 134.97 (e), 106.69 (e), 64.66 (e), 64.26 (e), 56.87 (e), 52.54 (o), 49.24 (e), 44.21 (e), 34.78 (e), 34.52 (e), 34.34 (e), 26.42 (e); MS (CI) m/z 297, 279; exact mass for $C_{15}H_{20}O_6$ (M) found 297.1332 (calcd 297.1338).

***trans*-1,2,3,4,4a,5,6,7,8,8aα-Decahydro-1α-[(dimethylphenylsilyl)methyl]-4$\alpha\beta$-[(methyloxy)carbonyl]-6,6-(ethylenedioxy)-2(1*H*)-naphthalenone (15b).** Ammonia (Matheson, ca. 20 mL) was condensed using a dry ice condenser in a flask at −78 °C. Finely divided lithium–1% sodium wire (Alfa) was then added until the blue color persisted to ensure that no water was present. At that stage lithium–1% sodium wire (5 mg, 0.7 mmol) was added to the solution which was stirred until the time of complete dissolution. The enone **9b** (100 mg, 0.24 mmol), diluted in THF (5 mL), was then added dropwise. TLC analysis of the reaction showed the UV activity of the starting material spot to vanish. Isoprene (Kodak) was cautiously added to discharge the blue color. The reaction was left for 20 min at −78 °C and then slowly brought to room temperature, allowing the

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ammonia to evaporate. Once most of the ammonia was gone, wet ether was added followed by saturated NH_4Cl and distilled water to dissolve the salts. Extraction with ether, concentration, and column chromatography (10% EtOAc in hexane) allowed isolation of the desired ketone (95 mg, 95%): IR (CCl_4) 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (3 H, m), 7.33 (2 H, br t), 3.97–3.78 (4 H, m), 3.70 (3 H, s), 3.27 (1 H, ABX m, J = 2.98, 8, 11), 2.32–2.00 (4 H, m), 1.81–1.69 (2 H, m), 1.60–1.31 (2 H, m), 1.29–1.16 (2 H, m), 0.96 (1 H, J = 2.98, 14.84, dd), 0.29 (3 H, s), 0.27 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.10 (e), 174.79 (e), 140.00 (e), 133.58 (o), 128.61 (o), 127.58 (o), 107.73 (e), 64.30 (e), 64.24 (e), 51.38 (o), 50.34 (o), 47.51 (e), 47.37 (o), 44.36 (e), 38.38 (e), 37.48 (e), 35.04 (e), 24.23 (e), 12.23 (e), -1.82 (o), -2.15 (o); MS (EI) m/z 416, 401, 339; exact mass for $C_{23}H_{32}O_5Si$ (M) found 416.2017 (calcd 416.2019).

***trans*-1,4,4a,5,6,7,8,8aα-Octahydro-2-(*tert*-butyldimethylsiloxy)-1α-[(dimethylphenylsilyl)methyl]-4aβ-[(methyloxy)carbonyl]-6,6-(ethylenedioxy)naphthalene (16b).** To ketone **15b** (125 mg, 0.29 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added Et_3N (Malinckrodt, 3 mL) followed by dropwise addition of TBDMSOTf. After a total of 40 drops, TLC analysis showed only the desired product. The reaction was quenched with saturated $NaHCO_3$ solution and extracted twice with CH_2Cl_2. Drying with $MgSO_4$, concentration, and column chromatography (5% EtOAc in hexane) yielded the desired silyl enol ether **16b** (144 mg, 90%): IR (CCl_4) 1734, 1714, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (2 H, m), 7.32 (3 H, m), 4.56 (1 H, J = 6.6, bd), 3.88–3.71 (4 H, m), 3.55 (3 H, s), 2.71 (1 H, m), 2.27 (1 H, J = 6.6, br q), 2.18 (1 H, J = 14.17, br dd), 2.45 (2 H, m), 1.83–1.51 (5 H, m), 1.37 (1 H, J = 15.06, 4.8, dd), 1.16 (1 H, J = 4.6, br dd), 1.12 (1 H, m), 1.05 (1 H, overlapping), 0.92 (9 H, s), 0.37 (3 H, s), 0.23 (3 H, s), 0.08 (3 H, s), 0.05 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.26 (e), 154.44 (e), 140.95 (e), 133.48 (o), 128.66 (o), 127.65 (o), 107.93 (e), 99.90 (o), 64.10 (e), 51.20 (o), 45.79 (e), 44.41 (o), 44.01 (e), 39.53 (o), 36.65 (e), 34.70 (e), 25.72 (o), 24.12 (e), 18.01 (e), 16.30 (o), -0.95 (o), -2.39 (o), -4.22 (o), -5.32 (o); MS (EI) m/z 530, 471, 135, 73; exact mass for $C_{29}H_{46}O_5Si_2$ (M) found 530.2867 (calcd 530.2884).

***trans*-1,4,4a,5,6,7,8,8aα-Octahydro-2-(*tert*-butyldimethylsiloxy)-1α-[(dimethylphenylsilyl)methyl]-4aβ-[(methyloxy)methyl]-6,6-(ethylenedioxy)naphthalene (17b).** To silyl enol ether **16b** (20 mg, 37 mmol) in acid-free THF (distilled and stirred with K_2CO_3 over 2 h) at 0 °C was added an excess of LAH and the mixture slowly warmed to room temperature over 8 h. The reaction was then cooled to 0 °C, and Gaubler's salt was added until a white precipitate formed. The solid was filtered and washed with a total of 50 mL of acid-free THF in five portions. Concentration in vacuo allowed the isolation of the desired alcohol. The crude mixture was dissolved in 10 mL of acid-free THF and cooled to 0 °C. Excess NaH (Aldrich) and catalytic amount of KH (Aldrich) were added to the solution. After 10 min, methyl iodide (Malinckrodt, excess) was added and the reaction warmed to room temperature. TLC showed the reaction to be complete after 30 min. After 3 h, the reaction was cooled to 0 °C and quenched with an NH_4Cl saturated solution. The aqueous phase was extracted three times with ether, dried with $MgSO_4$, filtered, and concentrated. Column chromatography (5% EtOAc in hexane) allowed isolation of the desired ether **17b** (9 mg, 47%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (2 H, m), 7.3 (3 H, m), 4.6 (1 H, J = 6.6, bd), 4.0–3.75 (4 H, m), 3.5 (1 H, J = 14, d), 3.25 (3 H, s), 3.2 (1 H, J = 14, d), 2.2–1.0 (remaining protons), 0.95 (9 H, s), 0.37 (3 H, s), 0.23 (3 H, s), 0.08 (3 H, s), 0.05 (3 H, s); MS (EI) m/z 516, 471, 135; exact mass for $C_{29}H_{48}O_4Si_2$ (M) found 516.3094 (calcd 516.3091).

Acknowledgment. We thank the National Institutes of Health (GM 42295) for support of this work. We are grateful to A. Rothwell for supplying mass spectra.

Supplementary Material Available: ^1H and ^{13}C NMR of all compounds described in the Experimental Section as well as COSY and HETCOR for **15b** and **16b** (19 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.

An Improved Method for the Synthesis of Enantiomerically Pure Amino Acid Ester Isocyanates

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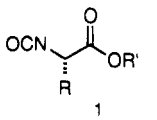
Received August 27, 1992

The isocyanate derivatives of amino acid esters (**1**) are useful as precursors to peptides[1] and azapeptides[2] and as synthetic building blocks.[3] These compounds are also



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potentially useful as chiral derivatizing agents[4] and for the preparation of chiral chromatographic media.[5] The most widely used preparation of amino acid ester isocyanates involves the continuous addition of a stream of gaseous phosgene to a refluxing suspension of the amino acid ester hydrochloride in toluene over a period of several hours.[1a,6] The hazards of handling gaseous phosgene, the high temperatures required to drive off the hydrogen chloride byproduct of the reaction, and the harshly acidic reaction conditions detract substantially from this procedure. Alternative procedures for the conversion of amino acid esters to isocyanates require multiple steps, elevated temperatures, or reagents that are expensive or not commercially available.[7,8]

In the course of preparing urea derivatives of amino acids, we required a convenient preparation of amino acid ester isocyanates.[9] We reasoned that elevated temperatures and the continuous addition of gaseous phosgene could be avoided by adding a base to remove hydrogen chloride. We have found that it is possible to generate amino acid ester isocyanates by addition of a commercially available solution of phosgene in toluene[10] to a mixture of an amino acid ester hydrochloride and pyridine (eq 1). The

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0022-3263/92/1957-7364$03.00/0