removal of almost all of the ethanol under reduced pressure, the mixture was extracted with AcOEt (3 × 5 mL). The combined extracts were washed with brine and dried (Na_2SO_4). The residue was purified by column chromatography (SiO_2, hexane–AcOEt = 20:1) to give 18.3 mg (27%) of **2a** as an oil.

Rearrangement of 1 with Ph_3SnH in 0.12 M Solution; Typical Procedure. A mixture of **1a** (R = C_6H_{13}, 110 mg, 0.42 mmol), Ph_3SnH (250 mg, 0.71 mmol), and AIBN (7 mg) in benzene (10 mL) was heated at reflux for 20 h. The mixture was concentrated and the residue was flash-distilled at 130–140 °C (10–20 Torr) to exclude tin reagents. The distillate was purified by column chromatography (SiO_2, hexane–AcOEt = 10:1–7:1) to give **3a** (27 mg, 50%) and **4a** (8 mg, 11%).

Spectral data of the compounds listed in Tables I and II are as follows.

3-Butyl-2-cyclohexenone (2b): bp 92–95 °C (26 Torr); IR (neat) 1671 (C=O), 1626 (C=C), 1458, 1255, 1195, 967, 888, 758 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 (t, J = 7.1 Hz, 3, CH_3), 1.21–1.55 (m, 4, CH_2), 1.90–2.00 (m, 2, CH_2), 2.16–2.37 (m, 6, CH_2), 5.86 (m, 1, HC=C); ^{13}C NMR (50 MHz) δ 13.80, 22.31, 22.69, 29.01, 29.63, 37.30, 37.74, 125.57, 166.81, 200.05.

3-Butylcyclohexanone (3b): bp 78–79 °C (14 Torr); IR (neat) 1715 (C=O), 1433, 1226, 731, 696 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (t, J = 6.5 Hz, 3, CH_3), 1.28 (m, 6, CH_2), 1.59–1.68 (m, 2, CH_2), 1.75 (m, 1, CH_2), 1.89 (d, J = 13.5 Hz, 1, CH_2), 1.97–2.02 (m, 1, CH_2), 2.00–2.06 (m, 1, CH_2CO), 2.22–2.28 (m, 1, CH_2CO), 2.34 (m, 1, CH_2CO), 2.42 (m, 1, CH_2CO); ^{13}C NMR (126 MHz) δ 14.02, 22.72, 25.32, 28.84, 31.32, 36.30, 39.07, 41.53, 48.26, 212.31.

2-Butyl-2-methylcyclopentanone (4b): bp 69–70 °C (14 Torr); IR (neat) 1740 (C=O), 1462, 1162, 1108, 1060, 808, 729, 665 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (t, J = 7.3 Hz, 3, CH_3), 0.99 (s, 3, CH_3), 1.08–1.16 (m, 1, CH_2), 1.24–1.31 (m, 3, CH_2), 1.33–1.42 (m, 2, CH_2), 1.67–1.73 (m, 1, CH_2), 1.82–1.94 (m, 3, CH_2), 2.16–2.32 (m, 2, CH_2CO); ^{13}C NMR (126 MHz) δ 13.99, 18.71, 21.84, 23.28, 26.48, 35.64, 36.40, 37.73, 48.31, 223.97.

3-Undecyl-2-cyclohexenone (2c): bp 159–161 °C (25 Torr); IR (neat) 1673 (C=O), 1628 (C=C), 1348, 1325, 1253, 1193, 967, 665 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (t, J = 7.0 Hz, 3, CH_3), 1.26 (m, 14, CH_2), 1.29 (m, 2, CH_2), 1.50 (m, 2, CH_2), 1.98 (m, 2, CH_2), 2.20 (t, J = 7.5 Hz, 2, CH_2), 2.28 (t, J = 6.1 Hz, 2, CH_2), 2.36 (m, 2, CH_2CO), 5.87 (s, 1, HC=C); ^{13}C NMR (126 MHz) δ 14.01, 22.67, 22.73, 26.92, 29.25, 29.31, 29.38, 29.49, 29.60, 29.66 (2 C), 31.89, 37.35, 38.08, 125.61, 166.81, 200.01. Anal. Calcd for $C_{17}H_{30}O$; C, 81.54; H, 12.07. Found: 81.56; H, 12.11.

3-Undecylcyclohexanone (3c): bp 150 °C (14 Torr); IR (neat) 1717 (C=O), 1466, 1226, 1058, 866, 729, 696 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (t, J = 7.0 Hz, 3, CH_3), 1.26 (m, 21, CH_2), 1.62–1.69 (m, 1, CH_2), 1.75 (m, 1, CH_2), 1.89 (m, 1, CH_2), 1.97–2.02 (m, 1, CH_2), 2.02–2.07 (m, 1, CH_2CO), 2.20–2.29 (m, 1, CH_2CO), 2.35 (m, 1, CH_2CO), 2.42 (m, 1, CH_2CO); ^{13}C NMR (126 MHz) δ 14.12, 22.68, 25.33, 26.65, 29.34, 29.58, 29.62 (2 C), 29.65 (2 C), 31.33, 31.90, 36.62, 39.09, 41.54, 48.25, 212.29. Anal. Calcd for $C_{17}H_{32}O$; C, 80.89; H, 12.78. Found: 81.15; H, 12.77.

2-Methyl-2-undecylcyclopentanone (4c): bp 131–133 °C (25 Torr); IR (neat) 1740 (C=O), 1464, 1162, 1064, 723 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (t, J = 7.0 Hz, 3, CH_3), 0.98 (s, 3, CH_3), 1.24 (m, 18, CH_2), 1.36 (m, 2, CH_2), 1.70 (m, 1, CH_2), 1.83–1.92 (m, 3, CH_2), 2.16–2.33 (m, 2, CH_2CO); ^{13}C NMR (126 MHz) δ 14.11, 18.72, 21.84, 22.68, 24.28, 29.34, 29.53, 29.60 (2 C), 29.64, 30.22, 31.90, 35.64, 36.68, 37.73, 48.35, 223.96.

3-Hexyl-2-cycloheptenone (2d): bp 120–123 °C (25 Torr); IR (neat) 1653 (C=O), 1456, 1346, 1201, 940, 884 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (t, J = 6.3 Hz, 3, CH_3), 1.28 (m, 6, CH_2), 1.46 (m, 4, CH_2), 1.77 (m, 2, CH_2), 2.17 (m, 2, CH_2), 2.40 (m, 2, CH_2), 2.56 (m, 2, CH_2CO), 5.90 (s, 1, HC=C); ^{13}C NMR (126 MHz) δ 14.02, 21.22, 22.51, 25.09, 27.51, 28.93, 31.60, 32.51, 41.09, 42.12, 129.13, 162.57, 204.27.

3-Hexylcycloheptanone (3d): bp 111 °C (14 Torr); IR (neat) 1700 (C=O), 1456, 1350, 1251, 727 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (t, J = 6.5 Hz, 3, CH_3), 1.25, 1.27 (m, 9, CH_2), 1.36–1.43 (m, 1, CH_2), 1.50–1.70 (m, 4, CH_2), 1.83–1.93 (m, 3, CH_2), 2.37 (dd, J = 14.1, 10.6 Hz, 1, CH_2CO), 2.44–2.49 (m, 3, CH_2CO); ^{13}C NMR (126 MHz) δ 14.07, 22.60, 24.40, 26.87, 28.54, 29.36, 31.78, 36.04, 36.86, 37.28, 43.90, 49.99, 214.90.

2-Hexyl-2-methylcyclohexanone (4d): bp 99–102 °C (14 Torr); IR (neat) 1709 (C=O), 1456, 1431, 1125, 986, 727, 698 cm^{-1}; ^1H NMR (200 MHz) δ 0.87 (t, J = 6.5 Hz, 3, CH_3), 1.02 (s, 3, CH_3), 1.26 (m, 9, CH_2), 1.36 (td, J = 14.0, 4.0 Hz, 1, CH_2), 1.50–1.57 (m, 1, CH_2), 1.69 (m, 2, CH_2), 1.78 (m, 2, CH_2), 1.92 (m, 1, CH_2), 2.28–2.34 (m, 1, CH_2CO), 2.37–2.48 (m, 1, CH_2CO); ^{13}C NMR (126 MHz) δ 14.05, 21.03, 22.53, 22.60, 23.64, 27.54, 29.95, 31.67, 37.54, 38.80, 39.46, 48.65, 216.36.

Acknowledgment. We are thankful to the SC-NMR Laboratory of Okayama University for experiments with the Varian VXR-500 instrument. H.K. appreciates generous encouragement from Professor T. Sekiba of Toyama National College of Technology.

Registry No. **1a**, 135480-94-3; **1b**, 135454-90-9; **1c**, 135454-91-0; **1d**, 135454-92-1; **2a**, 66262-12-2; **2b**, 6301-49-1; **2c**, 135454-93-2; **2d**, 135454-94-3; **3a**, 69824-93-7; **3b**, 39178-69-3; **3c**, 103539-05-5; **3d**, 135454-94-3; **4a**, 135454-95-4; **4b**, 72653-69-1; **4c**, 135454-96-5; **4d**, 135454-97-6; cobaloxime, 3252-99-1.

Supplementary Material Available: Spectral data of **2a**, **3a**, and **4a** and ^1H NMR spectra of the compounds **2b,d**, **3b,d**, and **4b–d** (9 pages). Ordering information is given on any current masthead page.

Oxidation of Alcohols Using Bis(trichloromethyl) Carbonate as Activator of Dimethyl Sulfoxide

Claudio Palomo,* Fernando P. Cossio, Jesús M. Ontoria, and José M. Odriozola

Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Aptdo. 1072, 20080-San Sebastián, Spain

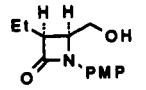
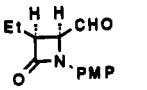
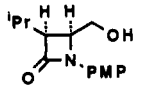
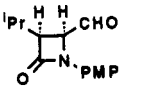
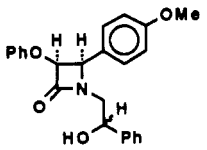
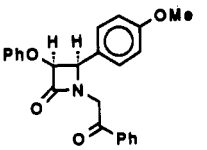
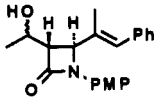
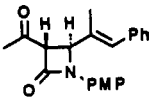
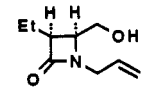
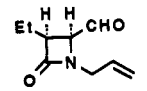
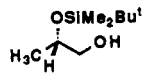
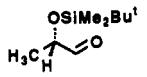
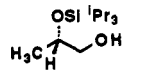
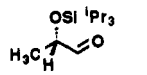
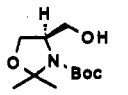
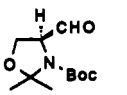
Received April 2, 1991

Mild oxidation of alcohols to carbonyl compounds is a very important synthetic operation in organic synthesis.[1] One useful method involves the combination of DMSO with a variety of electrophilic reagents.[2] DMSO–oxalyl chloride system,[3] DMSO–phosgene,[4] and DMSO–diphosgene dimer[5] have resulted in high yield conversions of alcohols to carbonyl compounds. However, the potential hazards associated with these reagents render them inappropriate for large-scale production of carbonyl compounds. In connection with studies directed toward the synthesis of (±)-PS-5 and (±)-PS-6 carbapenem antibiotics and their 6-epi analogues[6] we needed multigram quantities of aldehydes **8** and **9** (Scheme I). After examining some oxidizing reagents, we found that bis(trichloromethyl)carbonate (triphosgene), recently developed by Eckert and Forster,[7] is an excellent activator of DMSO to perform mild oxidations of alcohols to carbonyl compounds and this system is adaptable for a large-scale operations. Triphosgene, is a white crystalline solid, which has been successfully employed in a variety of synthetic transformations[7-10] as a safe alternative to phosgene and diphosgene dimer. Surprisingly, the oxidations of alcohols to carbonyl compounds promoted by triphosgene–DMSO has,

(1) For a recent review, see: Haines, A. H. In *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1988.
(2) For reviews, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. Tidwell, T. T. *Org. React.* **1990**, *39*, 297; *Synthesis* **1990**, 857.
(3) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(4) Barton, D. H. R.; Garner, B. J.; Wightman, R. H. *J. Chem. Soc.* **1964**, 1855.
(5) Takano, S.; Inomata, K.; Tomita, S.; Yanase, M.; Samizu, K.; Ogasawara, K. *Tetrahedron Lett* **1988**, *29*, 6619.
(6) Palomo, C.; Ontoria, J. M.; Odriozola, J. M.; Aizpurua, J. M.; Ganboa, I. *J. Chem. Soc., Chem. Commun.* **1990**, 248.
(7) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894.
(8) Daly, W. H.; Pouché, D. *Tetrahedron Lett.* **1988**, *29*, 5859.
(9) Coghan, M. J.; Caley, B. A. *Tetrahedron Lett.* **1989**, *30*, 2033.
(10) Jochims, J. C.; Hehl, S.; Herzberger, S. *Synthesis* **1990**, 1128.

0022-3263/91/1956-5948$02.50/0

Table I. Oxidation of Alcohols Using Triphosgene–DMSO System[a]

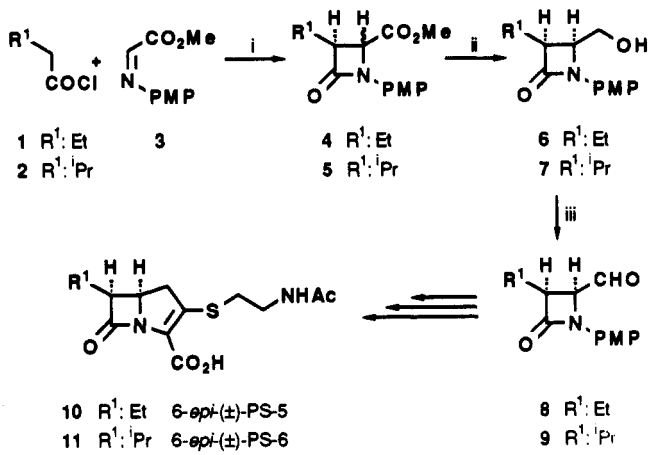
entry	substrate	product[b]	yield (%)[c]	bp (°C/Torr[d]) or mp (°C) (lit.)
a			82	86–89
b			80	96–98
c			95	97–99 (97–99)[17]
d			79	oil[18]
e			83	oil
f			83	94–95/10[e]
g			84	70–75/0.3[f]
h			81	70–75/0.02[g] (83–88/1.0–1.4)[20]

[a] Reactions conducted on a 10-mmol scale, except for entries a and b. [b] All compounds are racemic except entries f, g, and h. [c] Yield of pure isolated product checked by GLC/EIMS. [d] Oven temperature observed during distillation in a Kugelrohr apparatus. [e] $[\alpha]^{22}_D = -11.8°$ (c = 1.54, $CHCl_3$), lit.[19] $[\alpha]^{19}_D = -12°$ (c = 1.5, $CHCl_3$). [f] $[\alpha]^{22}_D = -6.3°$ (c = 1.07, CH_2Cl_2). [g] $[\alpha]^{20}_D = -93.3°$ (c = 1.47, $CHCl_3$), lit.[20] $[\alpha]_D = -91.7°$ (c = 1.34, $CHCl_3$).

to our knowledge, not been reported.

According to Scheme I, the starting β-lactams 4 and 5 were prepared in multigram quantities by our recently developed acid chloride–imino ester condensation[6] in 80–90% yields and usually as a mixture of cis and trans isomers at C_3–C_4 of the β-lactam ring. The major cis isomers ($J_{3,4} \approx 5$ Hz) were separated by crystallization from cyclohexane or by column chromatography and further treated with lithium borohydride[11] in refluxing tetrahydrofuran to furnish the hydroxymethyl derivatives 6 and 7 in excellent yields. Direct reduction of the methoxycarbonyl group to the corresponding aldehydes by the usual procedure[12] ($^iBu_2AlH$) was unfruitful, probably owing to the steric constraints imposed by the 3-alkyl substituent cis to the methoxycarbonyl group. Oxidation of these alcohols by treatment with triphosgene–DMSO[13] proceeded in good to excellent yields at −78 °C to room temperature in the presence of triethylamine. Although for 3 equiv of substrate 1 equiv of the reagent is enough to achieve a high yield oxidation process, yields were produced with a 2.5:1 reagent:substrate ratio. For example, compound 8 was obtained in 82% yield on a millimolar scale by using triphosgene:substrate in a 2.5:1 ratio while under theoretical amounts of triphosgene the oxidation was incomplete, and the starting hydroxy compound was partially recovered. Under the optimal reaction conditions, compound 9 was obtained from 7 on a decimolar scale in 80% isolated yield. In all cases, as judged by the coupling constants between C_2 and C_3 positions of the β-lactam ring, the relative cis stereochemistry was preserved during the oxidation process.

Scheme I[a]



1 R^1: Et 3 4 R^1: Et 6 R^1: Et
2 R^1: ^{i}Pr 5 R^1: ^{i}Pr 7 R^1: ^{i}Pr

10 R^1: Et 6-*epi*-(±)-PS-5 8 R^1: Et
11 R^1: ^{i}Pr 6-*epi*-(±)-PS-6 9 R^1: ^{i}Pr

[a] Reagents and conditions: (i) NEt_3, hexane, reflux, 12–15 h; (ii) $LiBH_4$, THF; (iii) $(Cl_3CO)_2O$–DMSO, CH_2Cl_2, −78 °C, then NEt_3, −78 → 20 °C. PMP = *p*-methoxyphenyl group.

Extension of the above procedure to a variety of structurally different hydroxy compounds is shown in Table I. As can be seen from the data listed in the Table I, the oxidation reaction works well with hydroxy compounds

(11) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.
(12) For a recent review, see: Cha, J. S. *Org. Prep. Proc. Int.* **1989**, *21*, 451.
(13) Since decomposition of triphosgene produces 3 equiv of phosgene, we have used a 2-fold excess of DMSO relative to the theoretical phosgene charge to ensure destruction of triphosgene.

having a variety of functional groups such as α-silyloxy, α-amino, and α-amido alcohols, to provide the corresponding α-silyloxy aldehydes and α-amino and α-amido carbonyl compounds in good to excellent yields. Furthermore, the optical purity of these compounds, as indicated by their specific optical rotation, shows that no epimerization occurred at the α-position to the nascent carbonyl carbon under the describe reaction conditions.[14] This reagent may also be a good substitute for trifluoroacetic anhydride–DMSO as well as acetic anhydride–DMSO often employed in such oxidation reactions. The former usually gives the corresponding oxidized products along with variable amounts of trifluoroacetate esters[15] and although the latter could be used for a large-scale oxidations, it suffers from long reaction time and also the formation of acetate esters as well as (methylthio)methyl ethers.[2] Oxidation of a 3-(1′-hydroxyethyl) β-lactam (entry d) and 1-allyl-3-ethyl-4-(hydroxymethyl)azetidin-2-one (entry e) without any detectable amounts of chlorinated products also shows the potential advantage of the triphosgene–DMSO system for other substrates sensitive to oxidizing reagents.[16]

As demonstrated here, large-scale oxidation of alcohols proceeded in excellent yield by the use of triphosgene as a substitute of phosgene or its analogues. Small-scale oxidation of alcohols can also be performed in excellent yields and simplified by the use of triphosgene because exact amounts of this reagent can be conveniently weighed.

Since DMSO-based reagents for oxidation of hydroxy compounds occasionally show substrate specificity, the introduction of new systems to increase the chemists' armamentarium of reagents is desirable. Consequently, triphosgene could be now used as safe activator of DMSO to perform Swern-type oxidations in both small- and large-scale operations.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Analytical TLC analyses were carried out with Merck F-254 silica gel plates. All β-lactams prepared are racemic mixtures. All the other starting materials used in this work were prepared by standard procedures. CH_2Cl_2, hexane, and THF were respectively distilled over P_4O_{10}, Na, and Na/benzophenone.

***cis*-3-Ethyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)-azetidin-2-one (4).** A solution of butanoyl chloride (1) (20.8 mL, 0.2 mol) in hexane (100 mL) was added dropwise to a solution of methoxycarbonyl *N*-(4-methoxyphenyl)imine **3** (19.32 g, 0.1 mol) and triethylamine (42 mL, 0.3 mol) in hexane (300 mL) at rt. The resulting mixture was stirred magnetically and refluxed overnight and then cooled to rt and diluted with CH_2Cl_2 (400 mL). The resulting solution was washed with water (400 mL), 1 N HCl (400 mL), and $NaHCO_3$ (400 mL, saturated solution). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvents at reduced pressure gave the crude β-lactam, which was purified by column chromatography (silica gel 70–230 mesh, CH_2Cl_2/hexane 1:1 as eluent). The title β-lactam was obtained as a mixture of cis and trans isomers in a 83:17 ratio, respectively; yield 23.7 g (90%). The cis isomer was separated by crystallization from cyclohexane: mp 81–82 °C; IR (KBr) ν 1733 cm^{-1} br (C=O); ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2 H, *J* = 9 Hz, Ar), 6.85 (d, 2 H, *J* = 9 Hz, Ar), 4.60 (d, 1 H, *J* = 6 Hz, CH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.50 (m, 1 H, CH), 1.87–1.77 (m, 1 H, *H*CH), 1.68–1.58 (m, 1 H, HC*H*), 1.08 (t, 3 H, *J* = 7.5 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.50; N, 5.32. Found: C, 63.64; H, 6.46; N, 5.27.

***cis*-3-Isopropyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (5).** The same procedure as above was followed, starting from methoxycarbonyl *N*-(4-methoxyphenyl)imine **3** (19.32 g, 100 mmol) and isovaleryl chloride (**2**) (24.4 mL, 200 mmol). The title β-lactam was obtained as a mixture of cis and trans isomers in a ratio 83:17, respectively; yield 24.4 g (88%). The cis isomer was separated by crystallization from cyclohexane: mp 119–120 °C; IR (KBr) ν 1748 and 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 2 H, *J* = 9 Hz, Ar), 6.85 (d, 2 H, *J* = 9 Hz, Ar), 4.58 (d, 1 H, *J* = 6 Hz, CH), 3.80 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.28 (dd, 1 H, *J* = 6 Hz, *J*′ = 10.8 Hz, CH), 2.15–2.07 (m, 1 H, CH), 1.20 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.91 (d, 3 H, *J* = 6.6 Hz, CH_3). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.90; N, 5.05. Found: C, 64,86; H, 6.77; N, 4.93.

***cis*-3-Ethyl-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (6).** $LiBH_4$ (3.27 g, 0.15 mol) was added at once to a solution of *cis*-3-ethyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (**4**) (26.3 g, 0.1 mol) in THF (250 mL), and the resulting mixture was stirred and heated at reflux for 1 h. The reaction mixture was cooled to rt and diluted with CH_2Cl_2 (250 mL). The resulting solution was slowly poured into 1 N HCl (250 mL). The organic layer was separated, washed with $NaHCO_3$ (250 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure, giving the title β-lactam, which was purified by crystallization in benzene, yield 18.82 g (80%): mp 102.5–104 °C; IR (KBr) ν 3388 (OH), 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 2 H, *J* = 8.7 Hz, Ar), 6.85 (d, 2 H, *J* = 8.7 Hz, Ar), 4.23–4.18 (m, 1 H, CH), 4.04–3.92 (m, 2 H, HCH), 3.77 (s, 3 H, OCH_3), 3.29–3.22 (m, 1 H, CH), 2.57 (s_{br}, 1 H, OH, exchanges with D_2O), 1.94–1.84 (m, 1 H, HCH), 1.81–1.69 (m, 1 H, HCH), 1.13 (t, 3 H, *J* = 7.5 Hz, CH_3). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.89; H, 7.31; N, 5.84.

***cis*-4-(Hydroxymethyl)-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (7).** The same procedure as above was followed, starting from *cis*-3-isopropyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (**5**) (27.7 g, 0.1 mol) and $LiBH_4$ (4.36 g, 0.2 mol). After 2.5 h the reaction as treated, giving the title compound, yield 20.7 g (83%): mp 97–100 °C (benzene/cyclohexane); IR (KBr) ν 3365 (OH), 1691 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 2 H, *J* = 9 Hz, Ar), 6.84 (d, 2 H, *J* = 9 Hz, Ar), 4.22–4.18 (m, 1 H, CH), 4.14–4.08 (m, 1 H, *H*CH, dd, *J* = 4 Hz, *J*′ = 12.2 Hz, in the presence of D_2O), 4.01–3.92 (m, 1 H, HC*H*, dd, *J* = 4.1 Hz, *J*′ = 12.2 Hz, in the presence of D_2O), 3.77 (s, 3 H, OCH_3), 3.01 (dd, 1 H, *J* = 5.6 Hz, *J*′ = 10.7 Hz, CH), 2.56–2.53 (m, 1 H, OH, exchanges with D_2O), 2.28–2.18 (m, 1 H, CH), 1.21 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.02 (d, 3 H, *J* = 6.5 Hz, CH_3). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.33; H, 7.58; N, 5.62.

***cis*-3-Ethyl-4-formyl-1-(4-methoxyphenyl)azetidin-2-one (8).** To a stirred solution of bis(trichloromethyl) carbonate (11.9 g, 40 mmol) in CH_2Cl_2 (120 mL) at −78 °C was added DMSO (17 mL, 0.24 mol). The reaction mixture was stirred for 15 min and then a solution of *cis*-3-ethyl-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one (**6**) (23.5 g, 0.1 mol) in CH_2Cl_2 (80 mL) was slowly added at the same temperature. After 15 min of stirring, triethylamine (39.2 mL, 0.28 mol) in CH_2Cl_2 (160 mL) was added dropwise, maintaining the temperature below −70 °C. After the addition, the resulting suspension was stirred at −78 °C for 5 min and then the acetone–dry ice bath was removed. The reaction mixture was stirred at rt for 2 h and then was washed with 1 N HCl (150 mL) and brine (3 × 400 mL). Evaporation of the solvent under reduced pressure gave a residue, which was purified by crystallization in hexane, yield 19.1 g (82%): mp 86–89 °C

(14) Diisopropylethylamine could also been employed as base in such an oxidation process. This hindered base is known to prevent racemization in other sensitive sustrates, see: Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.

(15) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

(16) For some solutions to circumvent the chlorination problem in Swern oxidations, see: (a) ref 2. (b) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1967**, *89*, 2416. (c) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. (d) Hung, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. (e) Liu, H.-J.; Nyangulu, J. M. *Tetrahedron Lett.* **1988**, *29*, 3169. (f) Smith, A. B.; Leenay, T. L.; Liu, H.-J.; Nelson, L. A. K.; Ball, R. G. *Tetrahedron Lett.* **1988**, *29*, 49.

(17) Cossío, F. P.; López, M. C.; Palomo, C. *Tetrahedron Lett.* **1987**, *43*, 3963.

(18) Palomo, C.; Cossío, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1989**, *54*, 5736.

(19) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1986**, 393.

(20) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(hexane); IR (CH_2Cl_2) ν 1751 (C=O), 1732 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.88 (d, 1 H, J = 3.6 Hz, CHO), 7.25 (d, 2 H, J = 9 Hz, Ar), 6.87 (d, 2 H, J = 9 Hz, Ar), 4.49 (dd, 1 H, J = 6.1 Hz, J' = 3.6 Hz, CH), 3.79 (s, 3 H, OCH_3), 3.58 (m, 1 H, CH), 1.87 (m, 1 H, HCH), 1.72 (m, 1 H, HCH), 1.10 (dd, 3 H, J = 8.4 Hz, J' = 6.4 Hz, CH_3). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.57; H, 6.32; N, 5.78.

***cis*-4-Formyl-3-isopropyl-1-(4-methoxyphenyl)azetidin-2-one (9).** The same procedure as above was followed, starting from *cis*-4-(hydroxymethyl)-3-isopropyl-1-(4-methoxyphenyl)-azetidin-2-one (7) (24.9 g, 0.1 mol), yield 19.8 g (80%): mp 96–98 °C (AcOEt/hexane); IR (KBr) ν 1749, 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 9.91 (d, 1 H, J = 4.2 Hz, CHO), 7.23 (d, 2 H, J = 9 Hz, Ar), 6.86 (d, 2 H, J = 9 Hz, Ar), 4.45 (dd, 1 H, J = 4.2 Hz, J' = 6.1 Hz, CH), 3.78 (s, 3 H, OCH_3), 3.37 (dd, 1 H, J = 6.1 Hz, J' = 10.8 Hz, CH), 2.20–2.08 (m, 1 H, CH), 1.22 (d, 3 H, J = 6.5 Hz, CH_3), 0.96 (d, 3 H, J = 6.5 Hz, CH_3). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00: H, 6.93; N, 5.66. Found: C, 68.42; H, 6.84; N, 5.69.

Acknowledgment. This work was supported by Comisión Interministerial de Ciencia y Tecnología (Project FAR:88-0393). Grants from the Eusko Jaurlaritza to J. M. Ontoria and from the Ministerio de Educación y Ciencia to J. M. Ordiozola are gratefully acknowledged.

Registry No. 1, 141-75-3; 2, 108-12-3; 3, 72079-55-1; *cis*-4, 127055-24-7; *trans*-4, 127055-25-8; *cis*-5, 128474-68-0; *trans*-5, 128474-79-3; *cis*-6, 128474-72-6; *cis*-7, 129374-75-0; *cis*-8, 128571-93-7; *cis*-9, 133505-01-8; (±)-PS-5, 92471-41-5; (±)-PS-6, 135682-87-0; DMSO, 67-68-5; 1-(4-methoxyphenyl)-3-(1-hydroxyethyl)-4-(1-methyl-2-phenylethenyl)azetidin-2-one, 100239-22-3; 1-allyl-3-ethyl-4-(hydroxymethyl)azetidin-2-one, 135614-56-1; 3-phenoxy-4-(4-methoxyphenyl)-1-(2-hydroxy-2-phenylethyl)azetidin-2-one, 93681-48-2; 2-[(*tert*-butyldimethylsilyl)oxy]propanol, 135614-57-2; 2-[(tri-*iso*-propylsilyl)oxy]-propanol, 135614-58-3; 2,2-dimethyl-3-(*tert*-butyloxycarbonyl)-4-(hydroxymethyl)-tetrahydro-oxazole, 108149-63-9; 3-phenoxy-4-(4-methoxyphenyl)-1-(phenylcarbonylmethyl)azetidin-2-one, 114497-93-7; 1-(4-methoxyphenyl)-3-acetyl-4-(1-methyl-2-phenylethenyl)azetidin-2-one, 123003-88-3; 1-allyl-3-ethyl-4-formylazetidin-2-one, 135614-59-4; 2-[(*tert*-butyldimethysilyl)-oxy]propanone, 87727-28-4; 2-[(tri-*iso*-propylsilyl)oxy]propanone, 135614-60-7; 2,2-dimethyl-3-(*tert*-butyloxycarbonyl)-4-formyl-tetrahydro-oxazole, 102308-32-7; bis(trichloromethyl)carbonate, 32315-10-9.

Supplementary Material Available: Experimental procedures and spectral data for products c–h listed in Table I and NMR spectra for products e and q (4 pages). Ordering information is given on any current masthead page.

Synthesis of (±)-Rubrynolide and a Revision of Its Reported Stereochemistry

Stephen K. Taylor,* Jeffrey A. Hopkins, and Katherine A. Spangenberg

Department of Chemistry, Hope College, Holland, Michigan 49423-3698

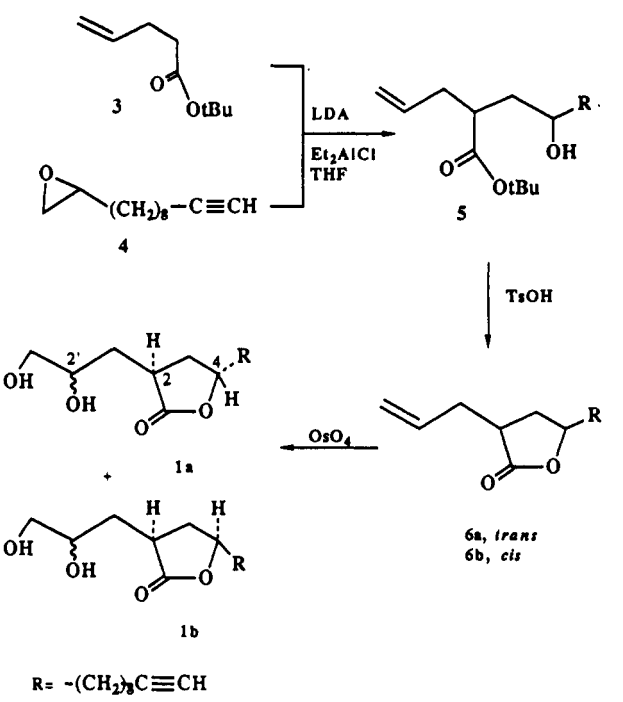
Douglas W. McMillen and John B. Grutzner

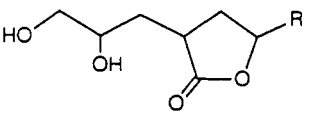
Department of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393

Received February 27, 1991

Rubrynolide (1) and rubrenolide (2), which represent a novel natural product type,[1] have been extracted as a 1:1 pair from the trunk of the Brazilian tree *Nectandra Rubra*.[1] Their biosynthesis has been discussed,[2] and they may represent interesting variants of biosynthetic routes to fatty acids.[1] An evaluation of their biological activity has been encouraged as a result of preliminary screening.[3] We herein describe the first synthesis of (±)-rubrynolide and confirm its proposed molecular connectivity.[1a] However, we revise the stereochemistry originally proposed for the 2,4-disubstituted lactone ring.[1b]

Scheme I





1, R = $(CH_2)_8$-C≡CH

2, R = $(CH_2)_8$-CH=CH_2

Our original plan was to synthesize both 1 and 2 from the enyne lactone 6 (Scheme I). Osmylation[4] of 6 would produce rubrynolide, and the selective reduction[5] of this product would produce rubrenolide. The key to this approach is a direct 1,3-asymmetric induction via an epoxide–aluminum enolate reaction that we demonstrated earlier.[6] The reported trans lactone stereochemistry could be achieved by reacting the favored *E* enolate of 3 with epoxide 4 (Scheme I). The ester enolate is of strategic importance here since, as a weak base, it will not abstract the acetylenic hydrogen of the epoxide and thereby cause side reactions.

The actual synthesis is outlined in Scheme I. The tosylate of 9-decen-1-ol (7) was treated with lithium acetylide–ethylene diamine complex. The resulting enyne 8 was epoxidized with *m*-CPBA. Epoxide 4 was then treated with the aluminum enolate[6] of *tert*-butyl 4-pentenoate to give predominantly the syn hydroxy ester 5 (syn/anti ratio

(1) (a) Franca, N. C.; Gottlieb, O. R.; Coxon, D. T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1972**, 514. (b) Franca, N. C.; Gottlieb, O. R.; Coxon, D. T. *Phytochemistry* **1977**, *16*, 257.

(2) (a) Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. (b) Filho, R. B.; Diaz, P. P.; Gottlieb, O. R. *Ibid.* **1980**, *19*, 455.

(3) (a) Gottlieb, O. R.; Mors, W. B. *J. Agric. Food Chem.* **1980**, *28*, 196. (b) Gottlieb, O. R. *J. Ethnopharm.* **1979**, *1*, 309.

(4) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973, (b) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

(5) (a) Lindlar, H.; Dubnis, R. *Org. Synth.* **1962**, *46*, 89. (b) Tedeschi, R. J.; Clark, G., Jr. *J. Org. Chem.* **1962**, *27*, 4323.

(6) Sturm, T.-J.; Marolewski, A. E.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039.

0022-3263/91/1956-5951$02.50/0