Formation of Stable Spiro[4.4] Ortho Ester Aminals during the Synthesis of the C_{26}−C_{32} Oxazole Fragment of Calyculin C

Petri M. Pihko and Ari M. P. Koskinen*

Department of Chemistry, University of Oulu, Linnanmaa, FIN-90570 Oulu, Finland

Maija J. Nissinen and Kari Rissanen

Department of Chemistry, University of Jyväskylä, P.O. Box 35, FIN-40351 Jyväskylä, Finland

Received August 17, 1998

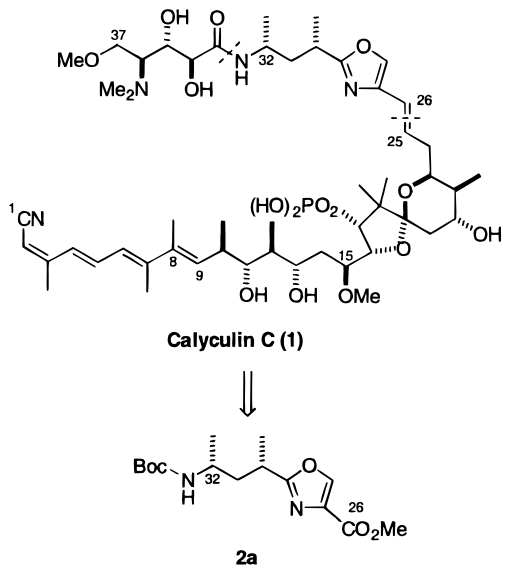
Ortho ester aminals (compounds with two nitrogen atoms and an oxygen atom bonded to a sp^3 carbon) are occasionally encountered as side products or intermediates in heterocycle syntheses,[1] in nucleotide chemistry,[2] and in flavonoid chemistry.[3] Open-chain ortho ester aminals are prone to disproportionation and further hydrolysis by water or alcohols, but the corresponding polycyclic ortho ester aminals are often stable enough to be isolated. In contrast to the ortho esters, which are rapidly gaining importance in organic synthesis,[4] the corresponding aminals have only scarcely been used, possibly due to their instability.

The reasons for the hydrolytic stability of the polycyclic ortho ester aminals relative to their open-chain counterparts have not been discussed in detail in the literature, although stereoelectronic effects are likely to play a central role.[5] The exo-anomeric effect has been invoked as an explanation for the stability of three simpler derivatives, a monocyclic ortho ester aminal and two spirocyclic analogues.[6] Herein, we report the facile formation of stable *spirocyclic* [4.4] ortho ester aminals and characterization of one isomer (**4b**) with X-ray crystallography. These compounds cannot benefit from anomeric stabilization (vide infra), and an alternative explanation for their stability as well as the lability of the open-chain derivatives is therefore required and presented.

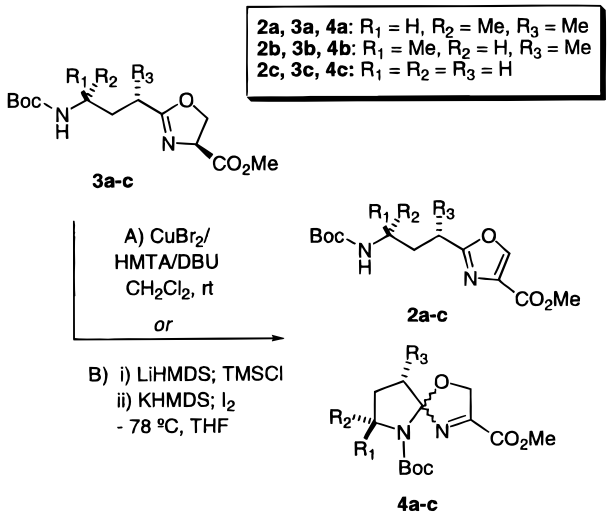
The final step of the synthesis of the C_{26}−C_{32} oxazole fragment (**2a**) of calyculin C (**1**)[7] (Scheme 1) requires the oxidation of the oxazolines **3a**/**3b** to the corresponding oxazoles **2a**/**2b** (Scheme 2).[8] Along with the desired oxazoles, *another set of diastereomeric compounds were formed in up to 52% yield* (Table 1). *To our surprise, these compounds proved to be the isomeric spirocyclic ortho ester aminals* (diastereomeric due to the presence of an additional chiral spiro atom) (**4a**, pure diastereomer; **4b**: **4b′**, 2:1 ratio).[9] Recrystallization afforded the pure diastereomer **4b** from the mixture **4b**/**4b′**.

Both oxidation methods employed[10] depend on the generation of the ester enolate and subsequent oxidative removal of the oxazoline ring hydrogen.[11] The formation of ortho ester aminals **4a**/**4b** in both cases indicates that

Scheme 1



Scheme 2



* To whom correspondence should be addressed. Phone: +358 8 553 1630. Fax: +358 8 553 1629. E-mail: Ari.Koskinen@oulu.fi.

(1) For examples, see: (a) Feinauer, R. *Angew. Chem.* **1966**, *78*, 938. (b) Doleschall, G.; Lempert, K. *Tetrahedron* **1968**, *24*, 5529−5545. (c) Fryer, R. I.; Earley, J. V.; Blount, J. F. *J. Org. Chem.* **1977**, *42*, 2212−2219. (d) Gotthardt, H.; Schenk, K.-H. *Angew. Chem.* **1985**, *97*, 604−606. (e) Knölker, H.-J.; Boese, R.; Döring, D.; El-Ahl, A.-A.; Hitzemann, R.; Jones, P. G. *Chem. Ber.* **1992**, *125*, 1939−1951. (e) Kappe, C. O.; Peters, K.; Peters, E.-M. *J. Org. Chem.* **1997**, *62*, 3109−3118. (f) Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, 75, 1264−1280, 1281−1294.

(2) For an example, see: Anzai, K.; Uzawa, J. *J. Org. Chem.* **1984**, *49*, 5076−5080.

(3) Lee, Y. T.; Fisher, J. F. *J. Org. Chem.* **1993**, *58*, 3712−3721.

(4) For a review of ortho esters, see: DeWolfe, R. H. *Synthesis* **1974**, 153−172. For recent use of ortho esters in synthesis, see: Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499−8502 and references therein.

(5) Poje, N.; Palkovic, A.; Poje, M. *J. Heterocycl. Chem.* **1997**, *34*, 477−483.

(6) (a) Bertolasi, V.; Ferretti, V.; Gilli, G.; Marchetti, P.; D'Angeli, F. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2135−2140.

(7) Isolation and characterization: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930−3932. For references to recent total or partial syntheses of calyculins, see ref 8.

(8) Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **1998**, *63*, 92−98.

(9) The isomer ratios were determined by ^{1}H NMR. At 365 K, **4a** gave only a single set of signals in ^{1}H and ^{13}C NMR. We are grateful to an anynomous reviewer for drawing our attention to this point.

(10) (a) Method A: Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W.; Kissick, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494−4496. (b) Method B: see ref 8.

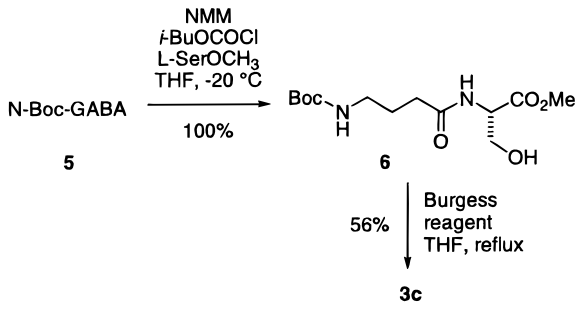
10.1021/jo981674j CCC: $18.00
Published on Web 01/05/1999

Table 1. Oxidation of Oxazolines 3a−c to the Oxazoles 2a−c and the Spiro Compounds 4a−c

substrate	conditions[a]	yield of oxazole (%)	yield of **4a**, **4b**/**4b′** or **4c**
2a	A	29	52
2a	B	42	25
2b	A	42	40
2b	B[b]	30	30
2c	A	30	35

[a] See Scheme 2. [b] NaHMDS was employed instead of LiHMDS in the first step.

Scheme 3



the carbamate proton can also be removed under these conditions, accompanied by ring closure and oxidation.

A detailed investigation into the mechanism is not possible at this time. We did, however, study the effect of the two methyl substituents (which were thought to facilitate the ring closure by the *reactive rotamer effect*[12]) by conducting the oxidation with the straight-chain oxazoline **3c** (Scheme 2), readily available from *N*-Boc-γ-aminobutyric acid **5** (*N*-Boc-GABA) (Scheme 3). Again, both the oxazole (**2c**) and the spirocyclic side product (**4c**) were formed in nearly equal amounts (Table 1), demonstrating that the 5-*exo*-*trig* ring closure leading to the spirocyclic structure occurs quite readily.

The compounds **4a**−**c** are remarkably stable to hydrolysis. They were isolated after normal aqueous workup[8] and could be readily purified by standard silica gel chromatography. However, examination of the possible anomeric *n*-σ* interactions within the spiro[4.4] system indicates that very little anomeric stabilization is expected. The only lone pairs available for the anomeric *n*-σ* interaction are the lone pairs of the ring oxygen (O(1), see Figure 1) and the sp^2 lone pair at N(1). No antiperiplanar orientation between the O(1) lone pairs and the two C−N σ bonds can be attained. The X-ray structure of **4b** (Figure 1)[13] substantiates this interpretation. The measured bond lengths of the two C(3)−N bonds are almost identical (1.439(7) Å and 1.435(6) Å). These values fit fairly well with the average C(sp^3)−N(sp^2) bond length of 1.454(11) Å of acyclic amides.[14,15] The relative

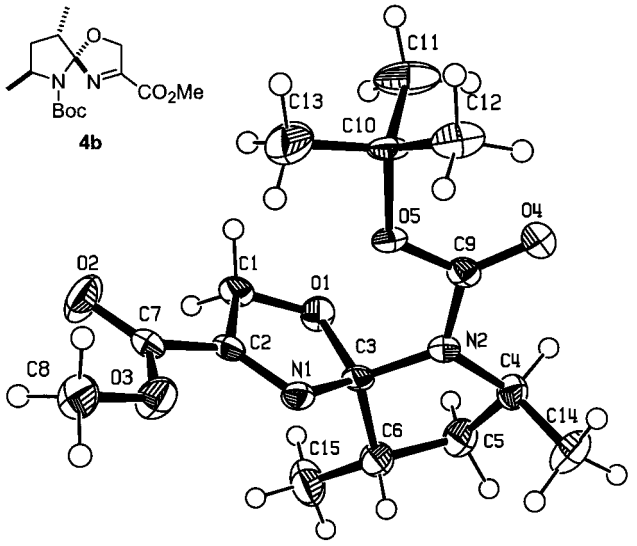
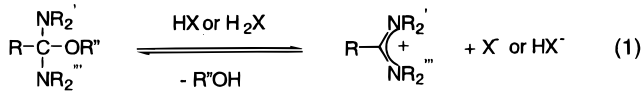


Figure 1. ORTEP plot of molecular structure of **4b**. Only one of the two crystallographically independent molecules is shown.

elongation of the C(3)−O(1) bond (bond length 1.453(7) Å) compared to the C(1)−O(1) bond (bond length 1.404-(6) Å) can be explained by a weak *n*-σ* interaction between the N(1) lone pair and the C(3)−O(1) bond.

Structures having three geminal heteroatoms, such as ortho ester aminals, react by the pathway that cleaves the weakest bond. In aminodihydroxymethane, ab initio calculations indicate that the most stable conformer does not possess maximal anomeric antiperiplanar interactions, resulting in *comparatively unreactive bonds*.[16,17] In the case of acyclic ortho ester aminals and aminodihydroxymethane, the stabilization of two C−X bonds gives rise to extreme polarization of the remaining C−X bond, thus lowering the activation energy for its cleavage. Acyclic ortho ester aminals typically react to give alkoxide and amidinium ions (eq 1):[18]



(1)

The relative stability of **4a**−**c** and related polycyclic ortho ester aminals[1−3] is attributed to geometric and stereoelectronic constraint—a diminished anomeric effect—

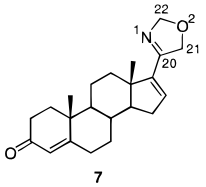
(11) A mechanistic rationalization involving two single-electron transfers (to Cu(II) or to I_2) is presented in ref 10a. These transfers are not necessarily synchronous.

(12) For a discussion of the reactive rotamer effect, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232.

(13) See the Supporting Information for the X-ray data. There are two crystallographically independent molecules in the unit cell, which have essentially identical geometries and bond lengths. In the text, only the dimensions of the molecule A are discussed.

(14) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1−S19.

(15) The bond lengths within the oxazoline ring are also very close to those measured for a 4-substituted Δ^3-1,3-oxazoline **7** (see Table 7 in the Supporting Information): Meetsma, A.; van Leusen, D.; van Leusen, A. M. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1993**, *49*, 351. This molecule was selected for comparison as it represents the least substituted Δ^3-1,3-oxazoline derivative in the Cambridge Crystallographic Data Centre archive (October 1997 release).



(16) (a) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 4048−4050. (b) Grein, F.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1562−1572.

(17) For a review of the anomeric effect and its effects on reactivity, see: Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: Oxford, 1996; pp 16−33 and references therein.

(18) Simchen, G. in *Methoden der Organischen Chemie (Houben-Weyl)*, Band E5; Falbe, J., Ed.; Georg Thieme Verlag: Stuttgart, 1985; pp 150−155.

imposed by the rigid spirocyclic structure. This reduction in the ionic character of the C−X bonds stabilizes the structure.

Experimental Section

General Methods. For the description of general experimental procedures, the solvents used, and for the preparation of compounds **2a,b**, **3a,b**, and **4a,b**, see ref 8.

(2*S*)-Methyl-2-[(4-((*tert*-Butoxycarbonyl)amino)-1-oxobutyl)amino]-3-hydroxypropionate (6). To a solution of **5** (2.03 g, 10.0 mmol, 100 mol %) in THF (150 mL) at −23 °C was added *N*-methylmorpholine (1.15 mL, 1.06 g, 10.5 mmol, 105 mol %), followed by isobutyl chloroformate (1.36 mL, 1.43 g, 10.5 mmol, 105 mol %). The resultant cloudy mixture was stirred at −23 °C for 15 min, and *l*-serine methyl ester hydrochloride (1.63 g, 10.5 mmol, 105 mol %) was then added, followed by *N*-methylmorpholine (1.15 mL, 1.06 g, 10.5 mmol, 105 mol %). The mixture was then allowed to warm slowly to room temperature. After 18 h, the mixture was quenched with 5% $NaHCO_3$ solution (300 mL) and extracted with EtOAc (6 × 100 mL). The combined extracts were dried (Na_2SO_4) and concentrated to afford **6** as a glass (3.03 g, 100%): $[\alpha]_D = -5.3$ ($c = 1.00$, MeOH); IR ($CDCl_3$) 3447, 2980, 1743, 1696, 1517, 1439, 1368, 1252, 1170, 1065 cm^{-1}; ^1H NMR (400 MHz) δ 6.96 (br d, 1 H, $J = 7.3$ Hz), 4.97 (m, 1 H), 4.62 (br d, 1 H, $J = 7.3$ Hz), 3.93 (m, 3 H), 3.74 (s, 3 H), 3.20 (m, 1 H), 3.11 (m, 1 H), 2.28 (app dt, 2 H, $J = 2.5$, 6.8 Hz), 1.87 (septet, 1 H, $J = 6.7$ Hz), 1.74 (br septet, 1 H, $J = 6.7$ Hz), 1.40 (s, 9 H); ^{13}C NMR (100 MHz) δ 172.8, 171.0, 156.7, 79.7, 62.7, 54.8, 52.5, 39.1, 32.9, 28.3, 26.1. Anal. Calcd for $C_{13}H_{24}N_2O_6$: C, 51.30; H, 7.95; N, 9.20. Found: C, 51.13; H, 8.23; N, 8.82.

(4*S*)-2-[3-((*tert*-Butoxycarbonyl)amino)propyl]-2-oxazoline-4-carboxylic Acid, Methyl Ester (3c). To a solution of dipeptide **6** (1.00 g, 3.29 mmol, 100 mol %) in THF (40 mL) at 0 °C was added Burgess reagent (1.02 g, 4.28 mmol, 130 mol %) over a period of 10 min, and the resulting solution was then allowed to warm to room temperature. After 1 h, the solution was heated to reflux for 3 h and allowed to cool. Evaporation of the solvent gave a residue that was partitioned between 10% MTBE/toluene (50 mL) and saturated NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with 10% MTBE/toluene (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash chromatography (4 × 16 cm silica, 100% EtOAc) to give **3c** as a colorless oil (0.53 g, 56%): $[\alpha]_D = +95.1$ ($c = 1.00$, MeOH); IR ($CDCl_3$) 3455, 2980, 1740, 1710, 1660, 1507, 1368, 1249, 1173 cm^{-1}; ^1H NMR (200 MHz) δ 4.74 (ddt, 1 H, $J = 1.1$, 7.6, 10.7 Hz), 4.49 (dd, 1 H, $J = 7.6$, 8.6 Hz), 4.40 (dd, 1 H, $J = 8.6$, 10.7 Hz), 3.79 (s, 3 H), 3.18 (q, 2 H, $J = 6.4$ Hz), 2.38 (dt, 2 H, $J = 1.1$, 7.0 Hz), 1.85 (qn, 2 H, $J = 7.0$ Hz), 1.44 (s, 9 H); ^{13}C NMR (100 MHz) δ 171.7, 170.3, 155.9, 79.2, 69.4, 68.0, 52.6, 39.8, 28.4, 26.1, 25.3; HRMS (CI, NH_3) calcd for MH^+ ($C_{13}H_{23}N_2O_5$) 287.1607, found 287.1602, $\Delta = 1.7$ ppm.

2-[3-((*tert*-Butoxycarbonyl)amino)propyl]-2-oxazole-4-carboxylic Acid, Methyl Ester (2c) and (±)-6-(1,1-Dimethylethyl) 3-Methyl-1-oxa-4,6-diazaspiro[4.4]non-3-ene-3,6-dicarboxylate (4c). To a suspension of $CuBr_2$ (1.47 g, 6.56 mmol, 400 mol %) in degassed CH_2Cl_2 (50 mL) at room temperature was added hexamethylenetetramine (920 mg, 6.56 mmol, 400 mol %) as a solid, followed by addition of DBU (980 μL, 1.00 g, 6.56 mmol, 400 mol %). The reaction mixture turned dark brown. After the mixture was cooled to 0 °C, a solution of oxazoline **3c** (470 mg, 1.64 mmol, 100 mol %) in degassed CH_2Cl_2 (15 mL) was added via cannula. The reaction mixture was allowed to warm to room temperature. After 2 h, a 1:1 solution of saturated NH_4Cl and 25% aqueous NH_3 (50 mL) was added, and the blue mixture was extracted with EtOAc (4 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The crude product thus obtained was purified by flash chromatography (3 × 17 cm of silica, linear gradient of 50% EtOAc/hexanes to 100% EtOAc) to afford the spirocyclic (±)-**4c** as an oil (138 mg, 30%), followed by oxazole **2c** as a colorless oil (162 mg, 35%). Data for **2c**: IR ($CDCl_3$) 3456, 2980, 1712, 1698, 1588, 1511, 1439, 1368, 1326, 1170, 1113 cm^{-1}; ^1H NMR (200 MHz) δ 8.16 (s, 1 H), 4.67 (m, 1 H), 3.20 (q, 2 H, $J = 6.6$ Hz), 2.87 (t, 2 H, $J = 7.5$ Hz), 1.99 (qn, 2 H, $J = 7.1$ Hz), 1.43 (s, 9 H); ^{13}C NMR (100 MHz) δ 168.9, 161.8, 155.0, 143.6, 133.1, 79.1, 52.0, 44.7, 41.8, 30.9, 28.3, 21.0, 18.8; HRMS (EI) calcd for M^+ ($C_{13}H_{20}N_2O_5$) 284.1372, found 284.1369, $\Delta = 1.1$ ppm. Data for (±)-**4c**: IR ($CDCl_3$) 2981, 1734, 1699, 1442, 1368, 1285, 1166, 1050 cm^{-1}; ^1H NMR (($CDCl_2$)$_2$, 365 K, 400 MHz) δ 5.00, (br d, 1 H, $J = 15.0$ Hz), 4.71 (d, 1 H, $J = 15.0$ Hz), 3.93 (s, 3 H), 3.67 (br dt, 1 H, $J = 10.5$, 6.4 Hz), 3.56 (dt, 1 H, $J = 10.5$, 7.1 Hz), 2.38 (dt, 1 H, $J = 13.2$, 7.9 Hz), 2.20 (qn, 1 H, $J = 6.4$ Hz), 1.99 (m, 2 H), 1.43 (s, 9 H); ^{13}C NMR (($CDCl_2$)$_2$, 365 K, 100 MHz) δ 163.6, 160.8, 152.4, 122.4, 79.9, 74.9, 52.4, 47.9, 39.6, 28.1, 21.0; HRMS (EI) calcd for MH^+ ($C_{13}H_{21}N_2O_5$) 285.1450, found 285.1401, $\Delta = 17$ ppm.

Data for 4a. (5*R*/*S*,7*R*,9*S*)-6-(1,1-Dimethylethyl) 3-methyl 7,9-dimethyl-1-oxa-4,6-diazaspiro[4.4]non-3-ene-3,6-dicarboxylate: colorless oil; $[\alpha]_D = -30.7$ ($c = 0.65$, MeOH); IR ($CDCl_3$) 2977, 1732, 1695, 1443, 1393, 1368, 1333, 1276, 1140, 1076 cm^{-1}; ^1H NMR (400 MHz, ($CDCl_2$)$_2$, 365 K) δ 5.00 (d, 1 H, $J = 15.0$ Hz), 4.66 (d, 1 H, $J = 15.0$ Hz), 3.95 (obs ddq, 1 H, $J = 9.1$, 5.9 Hz), 3.92 (s, 3 H), 2.36 (ddq, 1 H, $J = 12.0$, 7.0, 6.7 Hz), 2.20 (app dt, 1 H, $J = 12.0$, 6.7 Hz), 1.47 (obs ddd, $J = 12.0$, 9.1 Hz), 1.43 (s, 9 H), 1.37 (d, 3 H, $J = 5.9$ Hz), 0.89 (d, 3 H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, ($CDCl_2$)$_2$, 365 K) δ 163.4, 160.9, 152.7, 124.8, 79.6, 75.3, 53.6, 52.4, 43.3, 37.6, 28.2, 21.6, 12.4; HRMS (EI) calcd for M^+ ($C_{15}H_{24}N_2O_5$) 312.1685, found 312.1662, $\Delta = 7.4$ ppm.

Data for recrystallized, pure diastereomer 4b. (5*R*,7*S*,9*S*)-6-(1,1-Dimethylethyl) 3-methyl 7,9-dimethyl-1-oxa-4,6-diazaspiro[4.4]non-3-ene-3,6-dicarboxylate: $[\alpha]_D = +37.1$ ($c = 0.64$, MeOH); mp 93−95 °C (from Et_2O/isooctane); IR ($CDCl_3$, for a mixture of **4b**/**4b′**) 2977, 1732, 1697, 1442, 1393, 1367, 1295, 1147, 1070 cm^{-1}; ^1H NMR (400 MHz, ($CDCl_2$)$_2$, 370 K) δ 4.96 (d, 1 H, $J = 15.0$ Hz), 4.65 (d, 1 H, $J = 15.0$ Hz), 4.12 (app qn, 1 H, $J = 6.9$ Hz), 3.94 (s, 3 H), 2.81 (septet, 1 H, $J = 6.7$ Hz), 1.88 (dt, 1 H, $J = 8.1$, 12.0 Hz), 1.67 (dd, $J = 12.0$, 6.7 Hz), 1.42 (s, 9 H), 1.32 (d, 3 H, $J = 6.4$ Hz each), 0.87 (d, 3 H, $J = 6.7$ Hz); ^{13}C NMR (100 MHz, ($CDCl_2$)$_2$, 370 K) δ 164.0, 160.7, 152.7, 123.4, 79.7, 75.6, 53.6, 52.4, 41.3, 36.2, 28.1, 20.2, 11.2. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.40; H, 7.72; N, 8.84.

Acknowledgment. The authors wish to thank Mika Lindvall for very helpful comments, the Trace Element Laboratory of the University of Oulu for elemental analyses, Ms. Päivi Joensuu, University of Oulu, for the MS analyses, and the Academy of Finland and the Ministry of Education for financial support.

Supporting Information Available: Tables of crystal data, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **4b**, comparison of the bond lengths of **4b** to the oxazoline **7**, and copies of ^1H and ^{13}C spectra of **2c**, **3c**, **4a**−**c**, and **6** (22 pages). This material is contained in 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.

JO981674J