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Highly Stereoselective Synthesis of Exocyclic Tetrasubstituted Enol Ethers and Olefins. A Synthesis of Nileprost

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Abstract: A method for the stereoselective synthesis of cyano-substituted and methoxycarbonyl-substituted exocyclic enol ethers is described. The method involves the stereocontrolled reduction–isomerization of endocyclic enol ethers having a 1′-cyano-1′-alkenyl or 1′-methoxycarbonyl-1′-alkenyl functionality at C-2 as a key step. Treatment of these endocyclic enol ethers with 10 mol % of 10% Pd–C in toluene under H_2 (1 atm) at −40 to 0 °C afforded *E*-cyano-substituted or methoxycarbonyl-substituted exocyclic enol ethers stereoselectivity (≥10:1) in excellent yields. The methodology was applied to a synthesis of nileprost, a promising antiulcer agent, with a cyano-substituted exocyclic enol ether. Finally, this reduction–isomerization reaction was also applied to a stereoselective synthesis of the tetrasubstituted exocyclic olefins having a cyano functionality at C-1′ (≥8:1).

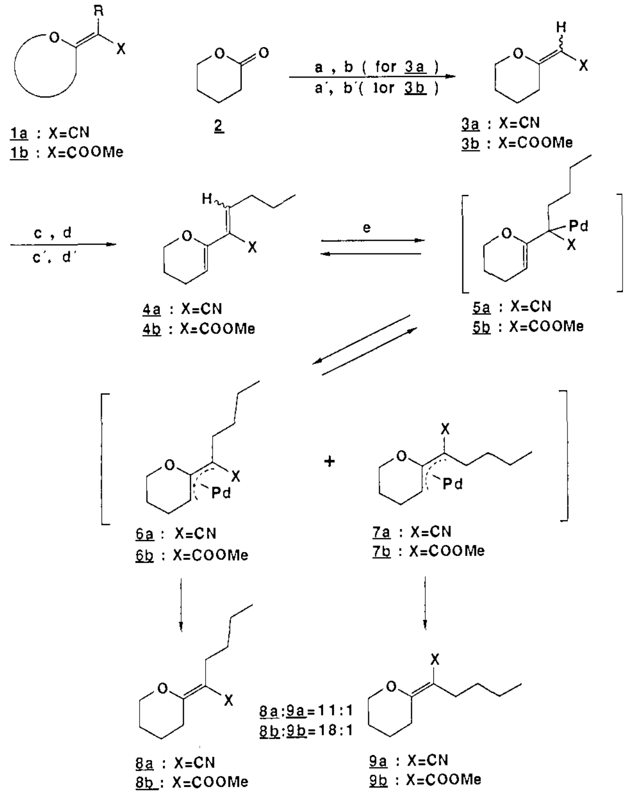
Although exocyclic enol ethers are readily available in a stereocontrolled manner,[1] the stereoselective synthesis of enol ethers of type **1** still remains a challenging problem in organic synthesis. The hitherto known method for the stereoselective synthesis of **1a** involves chlorosulfonyl isocyanate addition to enol ethers followed by treatment with triethylamine, affording **1a** in rather low yields.[2] On the other hand, addition of nitrile α-anions or ester enolate anions to lactones followed by dehydration gives **1** nonstereoselectively.[3] We report here a highly efficient synthesis of nileprost (**16**), a promising antiulcer agent[4] as well as a general method for the stereoselective synthesis of **1** and the exocyclic tetrasubstituted olefins **19a** and **22a**.

In the first place, development of an efficient method for the synthesis of **8a** was attempted. We envisioned that catalytic hydrogenation of **4a** using Pd–C[5] under H_2 would provide **8a** stereoselectively on the basis of the following:[6] First, at the initial step of hydrogenation, the σ-alkyl complex **5a**[7] would be regioselectively formed for the steric and electronic reasons.[8] Secondly, **5a** would lead to the more stable π-allyl complexes **6a** and **7a**, and formation of **6a** would be more favorable than that of **7a** for the steric and/or electronic reasons,[9] affording **8a** stereoselectively. Thirdly, **8a** would not undergo further hydrogenation due to steric factors (Scheme I).

Thus, **4a** (*E*:*Z* = 22:1) was regiospecifically synthesized from **2** in 56% overall yield (Scheme I). Hydrogenation of **4a** was carried out in MeOH using 10% Pd–C under H_2 at 22 °C for 10 min, and we were pleased to find that, as expected, **8a**[10] was formed stereoselectively (**8a**:**9a** = 6:1, 78%). In order to improve the stereoselectivity, we further investigated solvent effects as well as temperature effects. Among the conditions examined, reaction of **4a** in toluene (10 mol % of 10% Pd–C, 1 atm of H_2, −40 °C, 18 h) provided the best result (**8a**:**9a** = 11:1, 81%).[11] In contrast to these results, the use of Wilkinson's catalyst provided none of the products, and the use of platinum oxide in toluene gave **8a** and **9a** (2:1, 57%).[11]

The methodology was further applied to the stereoselective synthesis of **8b**. The diene **4b** (*E*:*Z* = 2:1), obtainable regiospecifically from **2** (54%, Scheme I), was subjected to reduction–isomerization reaction (Pd–C in toluene, −30 °C, H_2), giving **8b**[10] stereoselectively (**8b**:**9b** = 18:1, 80%).[11]

Scheme I[a]



[a] (a) CH_3CN, *n*-BuLi, THF, −78 °C; (b) MsCl, Et_3N, CH_2Cl_2, −78 °C; (c) LDA, THF, *n*-C_3H_7CHO, −98 °C; (d) MsCl, Et_3N, CH_2Cl_2, −78 °C; (e) H_2, 10% Pd–C, toluene, −40 °C or −30 °C: (a′) $TMSCH_2COOMe$, THF, LDA, −78 °C; (b′) AcOH, −78 °C to room temperature; (c′) LDA, THF, *n*-C_3H_7CHO, −78 °C; (d′) MsCl, Et_3N, CH_2Cl_2, −78 °C, then DBU, 0 °C.

Having established a method for the stereoselective synthesis of **8a**, development of an efficient synthesis of nileprost (**16**) was undertaken. Treatment of **12** (*E*:*Z* = 30:1), synthesized regiospecifically from **10** in 56% (Scheme II), with 10% Pd–C in toluene at −10 °C for 2 h (H_2) provided **14a**[10] in a ratio of 19(**14a**):1(**14b**) (98%).[11a] Likewise, **13** (*E*:*Z* = 13:1), obtainable regiospecifically from **11** (56%, Scheme II), was also transformed into **15a**[10] in a stereoselective manner (10% Pd–C in toluene, H_2, −10 °C, 40 min, **15a**:**15b** = 10:1, 98%).[11a] **15a** was then converted to **16** (24% overall yield) in a conventional way without any isomerization of the enol ether functionality. Thus, an efficient synthesis of **16**

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(3) (a) Japanese Unexamined Patent Publication, No. 102883, 1984. (b) Ger. Offen. 3. 322.893. (c) *Chem. Abstr.* **1985**, *103*, 592.

(4) Nickolson, R. C.; Town, M. H.; Vorbrüggen, H. *Med. Res. Rev.* **1985**, *5*, 1.

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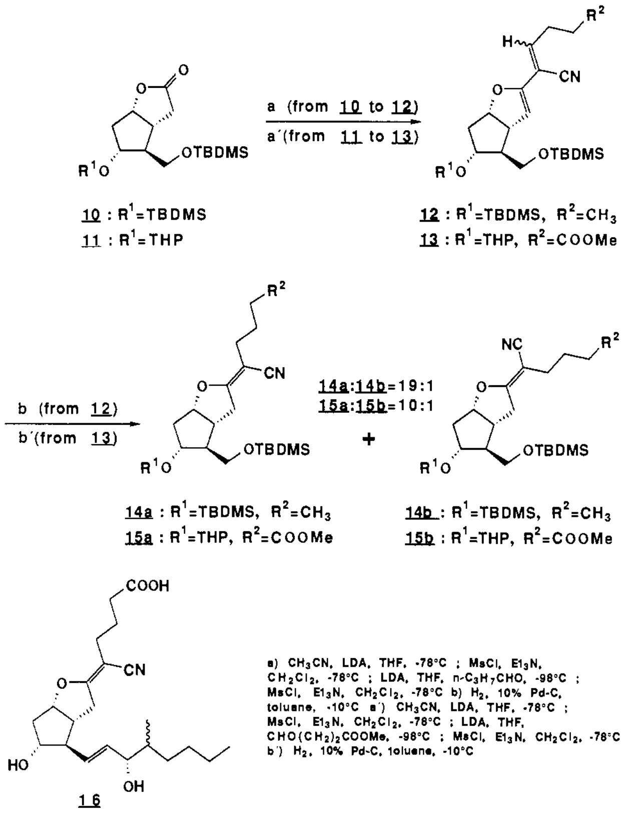
Scheme II[a]

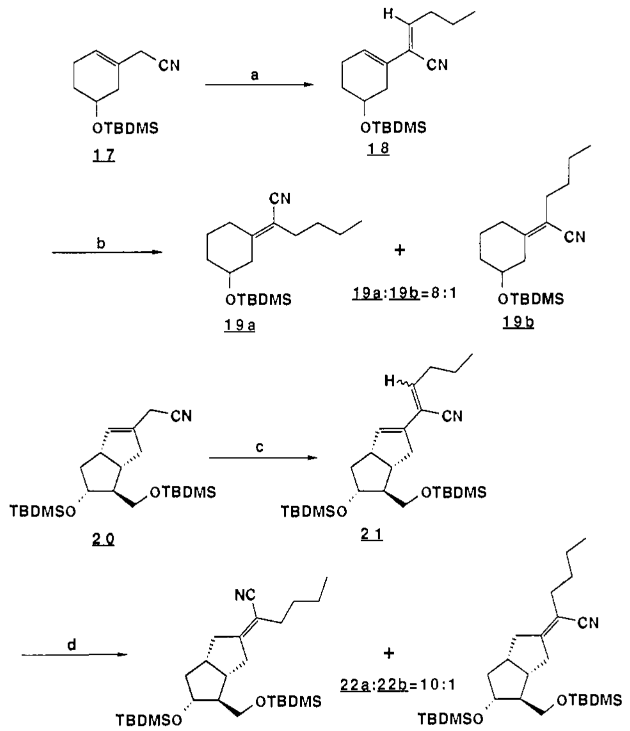


[a] (a) CH_3CN, LDA, THF, −78 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C; LDA, THF, n-C_3H_7CHO, −98 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C; (b) H_2, 10% Pd–C, toluene, −10 °C: (a′) CH_3CN, LDA, THF, −78 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C; LDA, THF, $CHO(CH_2)_2COOMe$, −98 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C; (b′) H_2, 10% Pd–C, toluene, −10 °C.

has been established (Scheme II).

In order to demonstrate the broad generality of the present methodology, we further investigated the reduction–isomerization reaction of the carbocycles **18** and **21**. Thus, **18** and **21** were first prepared regiospecifically from **17** and **20** in 93% and 87% yields, respectively (Scheme III). We were pleased to find that treatment of **18** with 10% Pd–C in mesitylene (−30 °C, 15 h, H_2) provided **19a**[10] stereoselectively (**19a**:**19b** = 8:1, 80%).[11] Furthermore, also in the case of **21** (E:Z = 1:30), **22a**[10] was formed stereoselectively (10% Pd–C in toluene, H_2, −40 °C, 4.5 h, **22a**:**22b** = 10:1, 66%).[11] Since the cyano functionality can be converted to many functionalities, the present reaction should be a useful method for the stereoselective synthesis of various tetrasubstituted exocyclic olefins.[12] On the other hand, Ar·Cr(CO)$_3$ catalyzed 1,4-hydrogenation reaction of **18** and **21** should give **19b** and **22b** in a stereocontrolled manner.[12a] Therefore, now, from the dienes **18** and **21** both the E- and Z-exocyclic olefins can be synthesized stereoselectively depending on the reaction conditions.

Scheme III[a]



[a] (a) LDA, THF, n-C_3H_7CHO, −78 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C, then −40 °C; (b) H_2, 10% Pd–C, mesitylene, −30 °C; (c) LDA, THF, n-C_3H_7CHO, −98 °C; MsCl, Et_3N, CH_2Cl_2, −78 °C, then 0 °C; (d) H_2, 10% Pd–C, toluene, −40 °C.

In conclusion, we have developed a conceptually new method for the stereoselective synthesis of **8**, **14a**, **15a**, **19a**, and **22a**. Application to the synthesis of other biologically interesting compounds as well as further mechanistic studies is under progress.

Experimental Section

2-(1-Cyano-1-pentenyl)-4,5-dihydropyran (4a). To a stirred solution of CH_3CN (1.56 mL, 30 mmol) in THF (25 mL) was added n-BuLi (1.82 mL, 29 mmol, 1.59 M hexane solution) at −78 °C, and the mixture was stirred for 0.5 h at the same temperature. To the lithiated acetonitrile solution was added δ-valerolactone (2.00 g, 20 mmol) in THF (20 mL) at −78 °C. After stirring for 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The crude oily residue (3.20 g) was dissolved in CH_2Cl_2 (40 mL), to which was successively added Et_3N (27.7 mL, 200 mmol) and $MeSO_2Cl$ (9.2 mL, 120 mmol) at −78 °C. After stirring for 0.5 h (−78 °C), the reaction mixture was quenched with ice–water, extracted with ether, successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (hexane–AcOEt, 5:1) to give **3a** in a ratio of 4(Z):1(E) as a colorless oil (2.22 g, 91%): for the E-isomer ^{1}H NMR ($CDCl_3$) δ 1.74–1.98 (m, 4 H), 2.40 (m, 2 H), 4.20 (m, 2 H), 4.32 (t, J = 1.0 Hz, 1 H); IR (neat) 2230, 1630 cm^{-1}; MS (m/z), 123 (M^+), 97 (M^+ − CN); HRMS (M^+) calcd for C_7H_9NO 123.0684, found 123.0681; for the Z-isomer ^{1}H NMR ($CDCl_3$) δ 1.68–1.96 (m, 4 H), 2.68 (m, 2 H), 4.09 (m, 2 H), 4.62 (t, J = 1.0 Hz, 1 H); IR (neat) 2220, 1630 cm^{-1}; MS (m/z), 123 (M^+), 97 (M^+ − CN); HRMS (M^+) calcd for C_7H_9NO 123.0684, found 123.0680.

To a stirred solution of **3a** (246 mg, 2.0 mmol) in THF (4 mL) was added LDA in THF (4 mL, 3.8 mmol) at −78 °C, and the mixture was stirred for 0.5 h at −78 °C. To the lithium anion solution was added butanal (288 mg, 4.0 mmol) in THF (4 mL) at −98 °C. After stirring for 10 min (−98 °C), the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, dried ($MgSO_4$), and concentrated. To a CH_2Cl_2 (6 mL) solution of the oily product (584 mg) was successively added Et_3N (2.77 mL, 20 mmol) and CH_3SO_2Cl (0.92 ml, 12.0 mmol) at −78 °C. After stirring for 15 min (−78 °C), the reaction mixture was quenched with ice–water, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:20) to give **4a** (E:Z = 22:1) as a colorless oil (225 mg, 64%): for the E-isomer

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(5) Palladium catalysts are prone to cause double-bond migration.

(6) Reduction of **4a** with Cu(I)H followed by protonation afforded **8a** and **9a** in a ratio of ca. 1:1, and Ar·Cr(CO)$_3$ catalyzed 1,4-hydrogenation of **4a** would afford **9a** stereospecifically.

(7) Siegel, S.; Smith, G. V. *J. Am. Chem. Soc.* **1960**, *82*, 6087.

(8) The effect of the enol ether funcionality was not clear at this stage. Considering only the steric factor, the σ-bond would be produced on the side chain. Furthermore, for more facile formation of the π-complex, **5a** would be formed regioselectively. See: Smith, G. V.; Roth, J. A. *J. Am. Chem. Soc.* **1966**, *88*, 3879.

(9) The cyano group is smaller than the alkyl group, and moreover it might be capable of complexing with palladium.

(10) The E-isomer was readily separated from the Z-isomer by silica gel column, and the stereochemistry was unequivocally determined by NOE.

(11) (a) The ratio was determined by HPLC. (b) A small amount of the saturated product and the trisubstituted olefin was also formed.

(12) (a) Shibasaki, M.; Sodeoka, M. *Tetrahedron Lett.* **1985**, *26*, 3491. (b) Corey, E. J.; Seibel, W. L. *Ibid.* **1986**, *27*, 905. (c) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65.

^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.7 Hz, 3 H), 1.40–1.68 (m, 2 H), 1.68–2.00 (m, 2 H), 2.08–2.26 (m, 2 H), 2.42 (m, 2 H), 4.08 (m, 2 H), 5.28 (t, *J* = 4.0 Hz, 1 H), 6.58 (t, *J* = 8.1 Hz, 1 H); IR (neat) 2220 1640 cm^{-1}; MS (*m*/*z*), 177 (M^+), 148, 135 (base peak); HRMS (M^+) calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1163; for the *Z*-isomer ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.7 Hz, 3 H), 1.41–1.51 (m, 2 H), 1.80–1.94 (m, 2 H), 2.09–2.25 (m, 2 H), 2.47 (m, 2 H), 4.05 (m, 2 H), 5.20 (t, *J* = 4.0 Hz, 1 H), 6.31 (t, *J* = 8.1 Hz, 1 H); IR (neat) 2220, 1640 cm^{-1}; MS (*m*/*z*), 177 (M^+), 148, 135 (base peak); HRMS (M^+) calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1150.

(*E*)-2-(1-Cyanopentylidene)tetrahydropyran (8a) and (*Z*)-2-(1-Cyanopentylidene)tetrahydropyran (9a). A suspension of **10%** Pd–C (21.0 mg, 0.02 mmol) in toluene (4 mL) was stirred for 40 min at 23 °C under 1 atm of H_2 pressure. To cooled (−40 °C) suspension was added **4a** (37 mg, 0.21 mmol, *E*:*Z* = 22:1) in toluene (4 mL), and the mixture was stirred for 18 h at the same temperature under 1 atm of H_2 pressure. The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (hexane–AcOEt, 15:1) to give **8a** (28.0 mg, 75%) as a colorless oil and **9a** (2.5 mg, 6.6%) as a colorless oil: for **8a** ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.28–1.50 (m, 4 H), 1.78 (m, 4 H), 2.16 (m, 2 H), 2.62 (m, 2 h), 4.05 (m, 2 H); IR (neat) 2200, 1630 cm^{-1}; MS (*m*/*z*), 179 (M^+), 136 (base peak), 111; HRMS (M^+) calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1301; for **9a** ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3 H), 1.26–1.57 (m, 4 H), 1.78–1.85 (m, 4 H), 2.08 (m, 2 H), 2.37 (m, 2 H), 4.09 (m, 2 H); IR (neat) 2220, 1630 cm^{-1}; MS (*m*/*z*), 179 (M^+), 136 (base peak), 111; HRMS (M^+) calcd for $C_{11}H_{17}NO$ 179.1310, found 179.1322.

2-(1-(Methoxycarbonyl)-1-pentenyl)-4,5-dihydropyran (4b). To a stirred solution of $(i\text{-}Pr)_2NH$ (4.6 mL, 33 mmol) in THF (20 mL) was added *n*-BuLi (1.6 M hexane solution, 20 mL, 32 mmol) at −78 °C. After stirring for 40 min at the same temperature, methyl(trimethylsilyl)acetate (4.80 g, 33 mmol) was gradually added, and the whole reaction mixture was stirred for 20 min (−78 °C). The resulting ester enolate solution was added to δ-valerolactone (2.20 g, 22 mmol) in THF (20 mL) at −78 °C. After stirring for 1.5 h (−78 °C), the reaction mixture was quenched with AcOH (5.06 mL), warmed to 0 °C, diluted with H_2O, and extracted with ether. The organic layer was successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The oily residue was purified by silica gel column chromatography (hexane–AcOEt, 5:1) to give **3b** (2.58 g, 75%) in a ratio of 1(*E*):1(*Z*) as a colorless oil: for the *E*-isomer ^{1}H NMR ($CDCl_3$) δ 1.68–1.92 (m, 4 H), 3.04 (m, 2 H), 3.65 (s, 3 H), 4.08 (m, 2 H), 5.28 (t, *J* = 1.0 Hz, 1 H); IR (neat) 1710, 1630 cm^{-1}; MS (*m*/*z*), 156 (M^+), 125 ($M^+ - OCH_3$), 96, 69 (base peak); HRMS (M^+) calcd for $C_8H_{12}O_3$ 156.0786, found 156.0781; for the *Z*-isomer ^{1}H NMR ($CDCl_3$) δ 1.74–2.00 (m, 4 H), 2.36 (m, 2 H), 3.65 (s, 3 H), 4.22 (m, 2 H), 4.88 (t, *J* = 1.0 Hz, 1 H); IR (neat) 1710, 1640, 1440 cm^{-1}; MS (*m*/*z*), 156 (M^+), 125 ($M^+ - OCH_3$), 96, 69 (base peak), 59; HRMS (M^+) calcd for $C_8H_{12}O_3$ 156.0786, found 156.0786.

To a stirred solution of **3b** (400 mg, 2.6 mmol) in THF (3 mL) was added LDA in THF (3 mL, 5.0 mmol) at −78 °C. After stirring for 50 min, butanal (461 mg, 6.4 mmol) in THF (3 mL) was added to the lithium anion solution (−78 °C). The whole reaction mixture was stirred at the same temperature for 20 min, quenched with saturated aqueous NH_4Cl, extracted with ether, successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. To a stirred solution of the oily residue (621 mg) in CH_2Cl_2 (5 mL) was successively added Et_3N (2.6 mL, 18.7 mmol) and CH_3SO_2Cl (0.5 mL, 6.2 mmol) at −78 °C, and the whole reaction mixture was stirred for 0.5 h. After addition of DBU (3.8 mL, 25.6 mmol), the reaction mixture was stirred for 20 min at 0 °C, quenched with ice–water, extracted with ether, successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:15) to give **4b** (407 mg, 76%) in a ratio of 2(*E*):1(*Z*) as a colorless oil: for the *Z*-isomer ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.6 Hz, 3 H), 1.24–1.64 (m, 2 H), 1.72–2.00 (m, 2 H), 2.00–2.28 (m, 4 H), 3.82 (s, 3 H), 4.08 (m, 2 H), 4.82 (t, *J* = 4.0 Hz, 1 H), 6.10 (t, *J* = 8.0 Hz, 1 H); IR (neat) 1720, 1670 cm^{-1}; MS (*m*/*z*), 210 (M^+), 178, 91, 77, 55, 41 (base peak); HRMS (M^+) calcd for $C_{12}H_{18}O_3$ 210.1255, found 210.1248; for the *E*-isomer ^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J* = 8.0 Hz, 3 H), 1.30–1.66 (m, 2 H), 1.80–2.00 (m, 2 H), 2.04–2.40 (m, 4 H), 3.76 (s, 3 H), 4.08 (m, 2 H), 4.60 (t, *J* = 4.0 Hz, 1 H), 6.88 (t, *J* = 8.0 Hz, 1 H); IR (neat) 1720, 1680, 1640 cm^{-1}; MS (*m*/*z*), 210 (M^+), 178, 91, 77, 55, 41 (base peak); HRMS (M^+) calcd for $C_{12}H_{18}O_3$ 210.1255, found 210.1262.

(*E*)-2-(1-(Methoxycarbonyl)pentylidene)tetrahydropyran (8b) and (*Z*)-2-(1-(Methoxycarbonyl)pentylidene)tetrahydropyran (9b). A suspension of 10% Pd–C (8 mg, 10 mol %) in toluene (2 mL) was stirred for 30 min at 23 °C under 1 atm of H_2 pressure. To a cooled (−30 °C) suspension was added **4b** (19 mg, 0.09 mmol, *E*:*Z* = 2:1) in toluene (2 mL), and the mixture was stirred for 13 h at −30 °C under 1 atm of H_2 pressure. The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (ether–hexane, 3:1) to give **8b** (15 mg, 80%) and **9b** (0.8 mg, 4%) as a colorless oil: for **8b** ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.0 Hz, 3 H), 1.10–1.48 (m, 4 H), 1.60–1.93 (m, 4 H), 2.33 (br t, *J* = 7.2 Hz, 2 H), 2.92 (m, 2 H), 3.70 (s, 3 H), 4.06 (m, 2 H); IR (neat) 1700, 1620 cm^{-1}; MS (*m*/*z*), 212 (M^+), 181 ($M^+ - OCH_3$), 169, 156, 137 (base peak), 109; HRMS (M^+) calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1416; for **9b** ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.0 Hz, 3 H), 1.20–1.48 (m, 4 H), 1.68–1.90 (m, 4 H), 2.20 (br t, *J* = 7.2 Hz, 2 H), 2.36 (m, 2 H), 3.72 (s, 3 H), 4.20 (m, 2 H); IR (neat) 1700, 1620 cm^{-1}; MS (*m*/*z*), 212 (M^+), 181 ($M^+ - OCH_3$), 169, 156, 137 (base peak), 109, HRMS (M^+) calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1416.

(1*S*,5*R*,6*S*,7*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-((*tert*-butyldimethylsilyl)oxy)-(*E*)-3-(1-cyanopentylidene)-2-oxabicyclo[3.3.0]octane (14a) and Its *Z*-Isomer (14b). A suspension of 10% Pd–C (17 mg, 10 mol%) in toluene (1 mL) was stirred for 1 h at 23 °C under 1 atm of H_2 pressure. To a cooled (−10 °C) suspension was added **12** (78 mg, 0.16 mmol, *E*:*Z* = 30:1) in toluene (3 mL), and the mixture was stirred for 2 h under 1 atm of H_2 pressure (−10 °C). The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (AcOEt–hexane, 1:20) to give **14a** (73 mg, 93 %) and **14b** (4 mg, 5%) as a colorless oil: for **14a** ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 12 H), 0.88 (s, 18 H), 0.90 (t, *J* = 8.0 Hz, 3 H), 1.15–1.60 (m, 4 H), 1.75 (m, 1 H), 1.83 (ddd, *J* = 3.0, 6.0, 14.0 Hz, 1 H), 2.02–2.22 (m, 2 H), 2.31 (ddd, *J* = 7.0, 7.0, 14.0 Hz, 1 H), 2.50–2.70 (m, 1 H), 2.85–3.08 (m, 2 H), 3.54 (dd, *J* = 4.4, 10.3 Hz, 1 H), 3.62 (dd, *J* = 4.4, 10.3 Hz, 1 H), 4.06 (ddd, each *J* = 6.6 Hz, 1 H), 4.90 (ddd, *J* = 2.6, 6.6, 6.6 Hz, 1 H); IR (neat) 2250, 1640 cm^{-1}; MS (*m*/*z*), 479 (M^+), 478 ($M^+ - 1$), 422 ($M^+ - {}^tBu$, base peak), 392, 290, 147, 89, 73; HRMS (M^+) calcd for $C_{26}H_{49}NO_3Si_2$ 479.3251, found 479.3263; for **14b** ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 12 H), 0.89 (s, 18 H), 1.00 (t, *J* = 8.0 Hz, 3 H), 1.15–1.60 (m, 4 H), 1.65–1.86 (m, 1 H), 1.86–2.10 (m, 3 H), 2.30 (ddd, *J* = 7.0, 7.0, 14.0 Hz, 1 H), 2.50–2.70 (m, 1 H), 2.70–2.90 (m, 2 H), 3.55 (d, *J* = 5.1 Hz, 2 H), 4.02 (ddd, each *J* = 6.6 Hz, 1 H), 4.90 (ddd, *J* = 3.0, 7.0, 7.0 Hz, 1 H); IR (neat) 2250, 1640 cm^{-1}; MS (*m*/*z*), 479 (M^+), 478($M^+ - 1$), 422 ($M^+ - {}^tBu$), 392, 290, 147, 89, 73 (base peak); HRMS (M^+) calcd for $C_{26}H_{49}NO_3Si_2$ 479.3251, found 479.3259.

(1*S*,5*R*,6*S*,7*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-(1-cyano-4-(methoxycarbonyl)-1-butenyl)-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]oct-3-ene (13). To a stirred solution of CH_3CN (830 mg, 20.3 mmol) in THF (20 mL) was added LDA (20 mmol) in THF (20 mL) at −78 °C. After stirring for 0.5 h at the same temperature, **11** (5.00 g, 13.5 mmol) in THF (15 mL) was added, the whole reaction mixture was stirred for an additional 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 2:1) to give the lactol (5.41 g, 98 %) as a colorless oil. To a stirred solution of the lactol (5.22 g, 12.7 mmol) in CH_2Cl_2 (20 mL) was successively added Et_3N (14.1 mL, 101 mmol) and CH_3SO_2Cl (1.93 mL, 25.4 mmol) at −78 °C. After stirring for 1 h (−78 °C), the reaction was quenched with ice–water, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:5) to give the α,β-unsaturated cyanide (4.66 g, 94 %) in a ratio of 1(*E*):2(*Z*) as a colorless oil. To a stirred solution of the α,β-unsaturated cyanide (300 mg, 0.76 mmol) in THF (2 mL) was added LDA (1.14 mmol) in THF (1.5 mL) at −78 °C. After stirring for 0.5 h, $CHO(CH_2)_2COOMe$ (220 mg, 1.9 mmol) in THF (2 mL) was added (−78 °C), and the whole reaction mixture was stirred at the same temperature for 10 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1:1) to give the coupling product (273 mg, 70 %) as a colorless oil. To a stirred solution of the coupling product (171 mg, 0.34 mmol) in CH_2Cl_2 (4 mL) was successively added Et_3N (0.7 mL, 5.1 mmol) and CH_3SO_2Cl (0.08 mL, 1.0 mmol) at −78 °C. After stirring for 0.5 h (−78 °C), the reaction mixture was quenched with ice–water, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 1:1) to afford **13** (153 mg, 91%) in a ratio of 13(*E*):1(*Z*) as a colorless oil: ^{1}H NMR (C_6D_6) δ 0.04 (s, 6 H), 0.90 (s, 9 H), 1.16–1.86 (m, 6 H), 3.10 (m, 1 H), 3.28 (s, 3 H), 3.34–3.60 (m, 3 H), 3.68–4.24 (m, 2 H), 4.74 (m, 2 H), 5.49, 5.56 (d and d, *J* = 3.0 Hz, total 1 H), 6.62, 6.63 (t and t, *J* = 7.5 Hz, total 1 H); IR (neat) 2220, 1740, 1640 cm^{-1}; MS (*m*/*z*), 491 (M^+), 460 ($M^+ - OCH_3$), 434 ($M^+ - {}^tBu$), 406, 350, 159, 85 (base peak); HRMS (M^+) calcd for $C_{26}H_{41}NO_6Si$ 491.2703, found 491.2714.

(1*S*,5*R*,6*S*,7*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-(*E*)-3-(1-cyano-4-(methoxycarbonyl)butylidene)-7-(tetrahydropyranyloxy)-2-oxabicyclo[3.3.0]octane (15a) and Its *Z*-Isomer (15b). A suspension of 10% Pd–C (22 mg, 10 mol %) in toluene (6 mL) was stirred at 23 °C for 1 h under 1 atm of H_2 pressure. To a cooled (−10 °C) suspension was added **13** (*E*:*Z* = 13:1, 75.6 mg, 0.15 mmol) in toluene (5 mL), and the mixture was stirred for 40 min (−10 °C). The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (ether–hexane, 1:3) to give **15a** (68.0 mg, 89%) and **15b** (7.0 mg, 9%) as a colorless oil: for **15a** ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.86 (s, 9 H), 1.30–2.42 (m, 15 H), 2.64 (m, 1 H), 3.00 (m, 2 H), 3.54 (m, 2 H), 3.66 (s, 3 H), 3.76 (m, 2 H), 4.60 (m, 1 H), 4.90, 4.98 (ddd and ddd, J = 2.0, 2.0, 6.0 Hz, total 1 H); IR (neat) 2220, 1740 1650 cm^{-1}; MS (m/z), 493 (M^+), 462 ($M^+ - OCH_3$), 436 ($M^+ - {}^tBu$), 320, 159, 85 (base peak); HRMS ($M^+ - {}^tBu$) $C_{22}H_{34}NO_6Si$ 436.2155, found 436.2156; for **15b** ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.36–2.70 (m, 16 H), 2.84 (m, 2 H), 3.39–3.68 (m, 3 H), 3.70 (s, 3 H), 3.94–4.18 (m, 2 H), 4.66 (m, 1 H), 5.00 (m, 1 H); IR (neat) 2220, 1740 1650 cm^{-1}; MS (m/z), 493 (M^+), 462 ($M^+ - OCH_3$), 436 ($M^+ - {}^tBu$), 352, 159, 85 (base peak); HRMS ($M^+ - {}^tBu$) calcd for $C_{22}H_{34}NO_6Si$ 436.2155, found 436.2149.

Conversion of 15a to Nileprost (16). To a stirred solution of **15a** (390 mg, 0.79 mmol) in THF (5 mL) was added $Bu_4N^+F^-$ (1 M THF solution, 1.58 mL, 1.58 mmol) at 23 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was quenched with brine, extracted with AcOEt, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 5:1) to give the alcohol (296 mg, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.20–2.80 (m, 17 H), 3.00 (m, 2 H), 3.60 (m, 2 H), 3.68 (s, 3 H), 3.76–4.28 (m, 3 H), 4.62 (m, 1 H), 4.94 (ddd, J = 3.0, 6.0, 8.0, 1 H); IR (neat) 3500, 2220, 1740, 1650 cm^{-1}; MS (m/z) , 379 (M^+), 348 ($M^+ - OCH_3$), 295 (M^+ − THP), 85 (base peak); HRMS (M^+) $C_{20}H_{29}NO_6$ 379.1995, found 379.1983.

To a stirred solution of the alcohol (296 mg, 0.78 mmol) in DMSO (3 mL) was successively added Et_3N (0.86 mL, 6.24 mmol) and SO_3·pyridine complex (992 mg, 6.42 mmol) in DMSO (3 mL) at 23 °C. After stirring at 23 °C for 40 min, the reaction mixture was quenched with ice–water, extracted with AcOEt, successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The aldehyde (312 mg) was obtained as a brown oil. On the other hand, to a stirred suspension of NaH (60% in oil, 62 mg, 1.56 mmol) in THF (3 mL) was added dimethyl (2-oxo-3-methylheptyl)phosphonate (460 mg, 1.95 mmol) in THF (6 mL) at 23 °C, and the whole reaction mixture was stirred for 1 h (23 °C). To this suspension was added the aldehyde (312 mg) in THF (5 mL) (23 °C). After stirring for 25 min (23 °C), the reaction was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether–hexane, 8:1) to give the α,β-unsaturated ketone (346 mg, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3 H), 1.10 (d, J = 7.6 Hz, 3 H), 1.18–2.84 (m, 23 H), 2.96 (m, 2 H), 3.68 (s, 3 H), 3.70–4.00 (m, 2 H), 4.10 (m, 1 H), 4.62 (m, 1 H), 4.96 (ddd, J = 3.0, 6.0, 6.0 Hz, 1 H), 6.30, 6.32 (d and d, J = 16.0 Hz, total 1 H), 6.72, 6.76 (dd and dd, J = 8.0, 16.0 Hz, total 1 H); IR (neat) 2200, 1740, 1690, 1650 cm^{-1}; MS (m/z), 487 (M^+), 403 (M^+ − THP), 372, 165, 85 (base peak); HRMS (M^+) calcd for $C_{28}H_{41}NO_6$ 487.2933, found 487.2929.

A solution of the α,β-unsaturated ketone (83 mg, 0.17 mmol) in THF (3 mL) and 65% aqueous CH_3COOH (3.5 mL) was heated at 55 °C for 5 h. The reaction mixture was neutralized by pouring into saturated aqueous $NaHCO_3$, extracted with ethyl acetate, washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography (ether) to give the hydroxy enone (61 mg, 89%): ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3 H), 1.12 (d, J = 7.6 Hz, 3 H), 1.20–2.84 (m, 19 H), 3.00 (m, 2 H) 3.70 (s, 3 H), 4.10 (ddd, each J = 7.9 Hz, 1 H), 4.98 (ddd, J = 2.0, 5.5, 5.5 Hz, 1 H), 6.34 (d, J = 16.0 Hz, 1 H), 6.74 (dd, J = 8.0, 16.0 Hz, 1 H); IR (neat) 3500, 2220, 1740, 1700, 1660 cm^{-1}; MS (m/z), 403 (M^+), 385 ($M^+ - H_2O$), 165, 43 (base peak), 18; HRMS (M^+) calcd for $C_{23}H_{33}NO_5$ 403.2139, found 403.2142.

To a stirred solution of 2,6-di-*tert*-butyl-4-methylphenol (398 mg, 1.81 mmol) in toluene (1.5 mL) was added DIBAH (1 M toluene solution, 1.34 mL, 1.34 mmol) at −10 °C, and the whole reaction mixture was stirred for an additional 1 h (−10 °C).[13] To the cooled (−78 °C) solution was added the hydroxy enone (54 mg, 0.13 mmol) in toluene (2 mL). After stirring for 2 h (−78 °C), the reaction mixture was gradually warmed to −20 °C (4 h), quenched with brine, extracted with AcOEt, successively washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel column chromatography to give the 15α-alcohol (30 mg, 56%) and the less polar 15β-alcohol (11 mg, 21%) as a colorless oil: for the 15α-alcohol ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6 H), 1.08–2.80 (m, 19 H), 2.86 (m, 2 H), 3.68 (s, 3 H), 3.94 (m, 2 H), 4.88 (ddd, J = 3.0, 6.0, 6.0 Hz, 1 H), 5.54 (m, 2 H); IR (neat) 3400, 2200, 1740, 1650 cm^{-1}; MS (m/z), 405 (M^+), 387 ($M^+ - H_2O$), 369 ($M^+ - 2H_2O$), 163, 79, 43 (base peak); HRMS ($M^+ - H_2O$) calcd for $C_{23}H_{33}NO_4$ 387.2410, found 387.2399.

A mixture of the 15α-alcohol (21 mg, 0.05 mmol), MeOH (1.5 mL), and 10% aqueous NaOH (1 mL) was stirred at 0 °C for 20 h. The reaction mixture was neutralized with 5% aqueous HCl, evaporated in vacuo, acidified with 5% aqueous HCl (pH 4), extracted with AcOEt, washed with brine, dried ($MgSO_4$), and concentrated to give nileprost (**16**) (20 mg, 100%) as a colorless viscous oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6 H), 1.05–1.60 (m, 8 H), 1.63–2.70 (m, 8 H), 2.93 (m, 2 H), 3.94 (m, 2 H), 4.85 (ddd, J = 3.0, 6.8, 6.8 Hz, 1 H), 5.60 (m, 4 H); IR (neat) 3450, 2200, 1710 cm^{-1}, MS (m/z), 391 (M^+), 373 ($M^+ - H_2O$), 363, 79, 43 (base peak), 18; HRMS (M^+) $C_{22}H_{33}NO_5$ 391.3964, found 391.3970. The spectral data described above were identical with those of an authentic sample, which was actually synthesized according to the literature.[2a,b]

2-[(*Z*)-1-Cyano-1-pentenyl]-4-((*tert*-butyldimethylsilyl)oxy)-1-cyclohexene (18). To a stirred solution of $(i\text{-}Pr)_2NH$ (152 mg, 1.50 mmol) in THF (8 mL) was added BuLi (1.6 M hexane solution, 0.86 mL, 1.38 mmol) at 0 °C. After stirring for 5 min, the mixture was cooled to −78 °C, and **17**[14] (314 mg, 1.25 mmol) in THF (6 mL) was added dropwise. After stirring for 20 min at the same temperature, butanal (181 mg, 2.50 mmol) was added and stirred for an additional 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated to give a colorless oily residue (465 mg). To a stirred solution of the residue (416 mg) in CH_2Cl_2 (10 mL) was successively added Et_3N (2.14 mL, 15.4 mmol) and CH_3SO_2Cl (0.60 mL, 7.75 mmol) at −78 °C. The reaction mixture was stirred for 30 min at the same temperature and warmed to 20 °C. After stirring for 4 h, the reaction mixture was diluted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–toluene, 4:1–3:1) to give **18** (319 mg, 93%) stereospecifically as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.84–1.06 (m, 12 H), 1.20–1.90 (m, 4 H), 1.90–2.60 (m, 6 H), 3.80–4.12 (m, 1 H), 6.04–6.32 (m, 2 H); IR (neat) 2220, 1635 cm^{-1}; MS (m/z), 305 (M^+), 304 (M^+ − H), 290, 248 (base peak); HRMS (M^+ − H) calcd for $C_{18}H_{30}NOSi$ 304.2097, found 304.2095.

(*E*)-1-(1-Cyano-1-pentylidene)-3-((*tert*-butyldimethylsilyl)oxy)cyclohexane (19a) and Its *Z*-Isomer (19b). A suspension of 10% Pd–C (5 mg, 7 mol %) in mesitylene (0.5 mL) was stirred at 23 °C for 30 min under 1 atm of H_2 pressure. To the cooled (−40 °C) suspension was added **18** (19 mg, 0.06 mmol) in mesitylene (0.7 mL), and the mixture was stirred for 15 h at −30 °C. The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated to give the oily residue, which was purified by silica gel column chromatography (hexane–toluene, 2:1) to give **19a** (14.0 mg, 72%) and a mixture of **19b** and the trisubstituted olefin derivative (ca. 1:1 from ^{1}H NMR analysis, 3.6 mg, 18%) as a colorless oil: for **19a** ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 0.93 (t, J = 7.0 Hz, 3 H), 1.30–1.59 (m, 6 H), 1.81–1.91 (m, 2 H), 2.11–2.35 (m, 4 H), 2.50–2.62 (m, 2 H), 3.69–3.75 (m, 1 H); IR (neat) 2230, 1635 cm^{-1}, MS (m/z), 308 (M^+ + H), 292, 250 (base peak), 223, 75; HRMS (M^+) calcd for $C_{18}H_{33}NOSi$ 307.2331, found 307.2316. The structure of **19b** was confirmed by ^{1}H NMR of the alcohol **19b′**, obtained by deprotection with TBAF in THF: for **19b′** ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3 H), 1.08–2.55 (m, 14 H), 2.95 (dd, J = 4.0, 13.0 Hz, 1 H), 3.68–4.01 (m, 1 H), MS (m/z) 193 (M^+), 175 ($M^+ - H_2O$), 164, 150 (base peak), 132, 107; HRMS ($M^+ - H_2O$) calcd for $C_{12}H_{17}N$ 175.1361, found 175.1343.

(1*S*,5*S*,6*S*,7*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-((*tert*-butyldimethylsilyl)oxy)-3-(1-cyano-1-pentenyl)bicyclo[3.3.0]oct-2-ene (21). To a stirred solution of $(i\text{-}Pr)_2NH$ (0.11 mL, 0.75 mmol) in THF (1 mL) was added *n*-BuLi (1.6 M hexane solution, 0.47 mL, 0.75 mmol) at 0 °C. After stirring for 10 min, **20**[12a] (197 mg, 0.47 mmol) in THF (1 mL) was added dropwise at −78 °C. After stirring for 30 min at the same temperature, butanal (68 mg, 0.94 mmol) was added at −98 °C and stirred for an additional 10 min at the same temperature. The reaction

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[13] (a) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*, 1363. (b) Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033.

[14] The compound **17** was prepared from the corresponding α,β-unsaturated ester by (1) DIBAH reduction in toluene, (2) Ph_3P, CBr_4 in CH_2Cl_2, and (3) KCN, 18-crown-6 in CH_3CN. See: (a) Sodeoka, M.; Satoth, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823. (b) Danishefsky, S.; Prisbylla, P. M.; Hiner, S. *Ibid.* **1978**, *100*, 2918.

J. Am. Chem. Soc. **1989**, *111*, 647-654

mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated to give a colorless oily residue. To a stirred solution of the residue in CH_2Cl_2 (4 mL) was successively added Et_3N (0.78 mL, 5.62 mmol) and CH_3SO_2Cl (0.11 mL, 1.41 mmol) at −78 °C. The reaction mixture was stirred for 10 min at the same temperature, and then for 20 min at 0 °C. The reaction mixture was quenched with ice–water, extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (hexane–ether, 10:1) to give **21** (196 mg, 88%) in a ratio of 1(*E*):30(*Z*) as a colorless oil: for the *Z*-isomer ^1H NMR ($CDCl_3$) δ 0.06 (s, 12 H), 0.88, 0.92 (s and s, total 18 H), 1.10–1.88 (m, 4 H), 2.00–3.30 (m, 7 H), 3.64 (d, *J* = 5.0 Hz, 1 H), 3.70 (d, *J* = 3.5 Hz, 1 H), 3.92 (ddd, *J* = 6.5, 8.5, 8.5 Hz, 1 H), 6.02 (d, *J* = 2.0 Hz, 1 H), 6.30 (t, *J* = 7.5 Hz, 1 H); IR (neat) 2250, 1460 cm^{-1}; MS (*m*/*z*), 460 (M^+ − Me), 418 (M^+ − ${}^tBu$, base peak), 286, 212, 186, 147, 117, 73; HRMS (M^+ − ${}^tBu$) calcd for $C_{23}H_{40}NO_2Si_2$ 418.2597, found 418.2568; for the *E*-isomer ^1H NMR ($CDCl_3$) δ 0.03, 0.06 (s and s, total 12 H), 0.84, 0.90 (s and s, total 18 H), 0.96 (t, *J* = 8.0 Hz, 3 H), 1.08–1.80 (m, 4 H), 1.96–2.90 (m, 7 H), 3.10 (m, 1 H), 3.62 (d, *J* = 5.5 Hz, 1 H), 3.63 (d, *J* = 4.0 Hz, 1 H), 3.91 (ddd, *J* = 7.0, 8.5, 8.5 Hz, 1 H), 6.02 (br s, 1 H), 6.10 (t, *J* = 7.8 Hz, 1 H); IR (neat) 2250, 1460 cm^{-1}; MS (*m*/*z*), 460 (M^+ − Me), 418 (M^+ − ${}^tBu$, base peak), 286, 147, 73; HRMS (M^+ − ${}^tBu$) calcd for $C_{23}H_{40}NO_2Si_2$ 418.2597, found 418.2574.

(1*S*,5*S*,6*S*,7*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-7-((*tert*-butyldimethylsilyl)oxy)-(*E*)-3-(1-cyanopentylidene)bicyclo[3.3.0]octane (22a) and Its *Z*-Isomer (22b). A suspension of 10% Pd–C (5 mg, 10 mol %) in toluene (0.5 mL) was stirred at 23 °C for 0.5 h under 1 atm of H_2 pressure. To a cooled (−40 °C) suspension was added **21** (22 mg, 0.05 mol, *E*:*Z* = 1:30) in toluene (1.5 mL), and the mixture was stirred for 4.5 h at −40 °C. The reaction mixture was filtered through silica gel and washed with ether. The combined filtrates were concentrated. The product was purified by silica gel column chromatography (hexane–ether, 25:1) to give **22** (15 mg, 66%, **22a**:**22b** = 10:1)[11a] as a colorless oil: for **22a**, ^1H NMR ($CDCl_3$) δ 0.04, 0.05 (s and s, total 12 H), 0.87, 0.89 (s and s, total 18 H), 0.92 (t, *J* = 7.0 Hz, 3 H), 1.35 (m, 3 H), 1.52 (m, 3 H), 2.15 (m, 3 H), 2.23–2.65 (m, 5 H), 2.82 (m, 1 H), 3.55 (d, *J* = 6.0, 10.0 Hz, 1 H), 3.64 (d, *J* = 6.0, 10.0 Hz, 1 H), 3.91 (ddd, each *J* = 7.0 Hz, 1 H); IR (neat) 2250, 1480 cm^{-1}; MS (*m*/*z*), 477 (M^+), 462 (M^+ − Me), 420 (M^+ − ${}^tBu$), 288, 214, 189, 147, 133, 73; HRMS (M^+) calcd for $C_{27}H_{51}NO_2Si_2$ 477.3458, found 477.3443; for **22b** ^1H NMR ($CDCl_3$) δ 0.04, 0.05 (s and s, 12 H), 0.87, 0.89 (s and s, 18 H), 0.92 (t, *J* = 7.5 Hz, 3 H), 1.33 (m, 3 H), 1.52 (m, 3 H), 2.15 (m, 3 H), 2.25–2.85 (m, 6 H), 3.60 (d, *J* = 5.0 Hz, 2 H), 3.99 (ddd, each *J* = 7.0 Hz, 1 H); IR (neat) 2250, 1480 cm^{-1}; MS (*m*/*z*), 477 (M^+), 462 (M^+ − Me), 420 (M^+ − ${}^tBu$), 288, 214, 189, 147, 133, 73; HRMS (M^+) calcd for $C_{27}H_{51}NO_2Si_2$ 477.3458, found 477.3476.

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Novel Sponge-Derived Amino Acids. 5.[1] Structures, Stereochemistry, and Synthesis of Several New Heterocycles

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Abstract: This paper reports the complete amino acid chemistry of an undescribed Jaspidae sponge, collected annually in the Benga lagoon of the Fiji Islands during the period from 1984 to 1987. Five different amino acid types are represented among its constituents and they include the bengamides (six compounds), isobengamide E, bengazoles (A and B), a diketopiperazine *cyclo*(L-*trans*-(4-hydroxyprolinyl)-L-phenylalanine), and *N*-acetyl-L-phenylalanine methyl ester. The structures and stereochemical features of the bengamides were established by relying on analogies to bengamides A and B, along with insights gained by extensive spectroscopic and chemical degradation of isobengamide E and bengamide E. The chirality of the substituted ε-caprolactam ring of the bengamides was established as 10*S* and 13*S* by a combination of molecular mechanics calculations and hydrolysis of isobengamide E and bengamide E fragmentation products to obtain L-lysine hydrochloride. The relative stereochemistry of the 2(*R**)-methoxy-3(*R**),4(*S**),5(*R**)-trihydroxy-8-methylnon-6(*E*)-enoyl side chain of the bengamides was based on analysis of ^1H NMR *J* values of cyclized products. The bengazole structures have been previously established, and the structures of the remaining two amino acids were verified by synthesis. Biogenetic pathways are suggested for each of the most novel amino acid types.

The study of nitrogen-containing heterocycles from Choristid sponges is a subject to which we and others are now devoting attention. The taxa from three families within this order, Jaspidae, Geodiidae, and Kallapididae, seem especially important because their multifarious natural products are almost always accompanied by exciting biological activity.[2] A few years ago we began a study of an encrusting, globular, orange, undescribed Jaspidae sponge that was prominent in the coral reef communities throughout Fiji. Our early collections had extracts with potent anthelmintic activity that afforded atypical amino acid derivatives, bengamides A and B,[3] as the only active constituents obtainable in large enough amounts to permit structural characterization. Faint ^{13}C NMR resonances between 40–60 and 150–180 ppm could be observed in anthelmintic-active solvent-partition fractions which intimated that other bioactive amino acids might be present.

During the past 2 years we have obtained this sponge from many Fiji locations. By contrast, our pursuit of this sponge from locations outside of Fiji were unsuccessful as it could not be located in nearby south Pacific areas ranging from Tonga to Vanuatu to the Solomon Islands. It now seems appropriate to give a complete account of the remarkable chemistry of this sponge because it ranges from bengamides A (**1**) and B (**2**)[3] to bengamides C–F (**3–6**), isobengamide E (**7**), bengazoles A (**8**) and B (**9**)[4], di-

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(1) Previous papers in this series are part 4, ref 17; part 3, ref 4; part 2, ref 3; and part 1, ref 2a.

(2) Recent examples of novel cytotoxins are jasplakinolide [= jaspamide] from *Jaspis johnstoni* [Jaspidae]: (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 3123. (c) Braekman, J. C.; Daloze, D.; Moussaiaux *J. Nat. Prod.* **1987**, *50*, 994. Calyculin A from *Discodermia calyx* [Kallapsidae]: (d) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujiti, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780. The geodiamolides from *Geodia* sp. [Geodiidae]: (e) Pettit, G. R., Rideout, J. A., Hasler, J. A. *J. Nat. Prod.* **1981**, *33*, 588. (f) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. J. *J. Org. Chem.* **1987**, *52*, 3091. The discodermins from *Discodermia kiiensis* [Geodiidae]: (g) Matsunaga, S.; Fusetani, N.; Konosu, S. *Tetrahedron Lett.* **1985**, *26*, 855.

(3) Quiñoá, E.; Adamczeski, M.; Crews, P. *J. Org. Chem.* **1986**, *51*, 4494.

(4) Adamczeski, M.; Quiñoá, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598.

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