A Facile Stereoselective Synthesis of (3a*R**,4*R**,6a*S**)-4-(Hydroxymethyl)-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one and Other Useful Cyclopentanoid Building Blocks†

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Various vicinally disubstituted cyclopentanone and cyclopentenone natural products, like prostaglandin A, preclavulone A, and *epi*-jasmonic acid, possessing either *trans* or *cis* stereochemistry of the side chains display various biological activities and have been major synthetic targets over many years.[1] Syntheses of *cis*-disubstituted cyclopentanoids have stricter stereochemical requirements than the thermodynamically more stable *trans*-disubstituted systems; therefore, the former compounds often have required synthetic approaches different from those usually employed in preparing prostaglandin-like *trans* compounds.[1]

In this paper, we describe a short and easily stereocontrolled prostaglandin-like synthesis of bicyclic lactone **1** and its further elaboration to other cyclopentanoid building blocks, such as **27** and **28**, which are key intermediates for the syntheses of compounds of the 12-oxophytodienoic acid cascade.[2] The present approach is based on lactone **2** which was readily prepared in multigram scale by a regiocontrolled Baeyer–Villiger oxidation of *cis*-bicyclo[3.3.0]octane-3,7-dione (**3**).[3]

Results and Discussion

Our plan involved either olefin **4** or **5** as a suitable intermediate for the conversion of **2** to the targeted lactone **1**. In order to explore the nontrivial regioselective reduction of ketone **2**, we initially performed semiempirical MO calculations (MNDO, AM1, and PM3)[4a] on **4**, **5**, and their simple derivatives **6**–**9** (no counterion was considered). The calculated standard heats of formation ($\Delta H_f°$) were very similar for structures **4** and **5** ($\Delta\Delta H_f° \leq 0.1$ kcal mol^{-1}) and **6** and **7** ($\Delta\Delta H_f° \leq 0.45$ kcal mol^{-1}); by contrast, we found that the *anti* dianion **8** is energetically much more stable than the *syn* isomeric structure **9** ($\Delta\Delta H_f° = 7$ kcal mol^{-1}),[4b,c] suggesting that the regioselective conversion of **2** to olefin **4** might be accomplished if a species like **8** was involved in this transformation. Thus, in order to mimic the electronic distribution in dianion **8**, tosylhydrazone **10**, easily prepared from ketone **2** ($TsNHNH_2$, THF, anhydrous $LaCl_3$ (1 equiv), 99%) was submitted to the Shapiro reaction[5,6] by using an excess of LDA or LHMDS. Under these conditions, decomposition of **10** must proceed through the intermediacy of trianion **11** or **12**,[6] to yield ultimately olefin **4** or **5**, respectively. Even if the factors controlling the regioselectivity of the Shapiro reaction on α,α′-dimethylene systems such as **10** are still rather puzzling,[7] we thought it is likely that electronic and electrostatic effects involved in determining the ratio of **11** to **12** would have been similar, at least in part, to those governing the relative stability of **8** and **9**. Therefore, we expected that deprotonation of tosylhydrazone **10** would have yielded trianion **11** as a major intermediate, and then lactone **4** as the more abundant alkene product. In the event, when tosylhydrazone **10** was exposed to LDA or LHMDS, either in the presence or in the absence of strongly cation-coordinating species like TMEDA,[6,8] the Shapiro reaction exibited virtually no regioselectivity and afforded olefins **4** and **5** in equal amounts. The issue of regioselectivity was then addressed for various 1,2-elimination reactions (Table 1) of simple derivatives (**14**–**18**) of alcohol **13**.[9] In particular, under reaction conditions favoring the E1cb mechanism (entries 6, 7, and 10 in Table 1), olefin **4** was expected to be formed in larger amounts than the regioisomer **5** since the kinetic deprotonation of **16** or **17** with an excess of a strong anionic base in polar solvents should occur more easily through the intervention of species like **19** than through the intervention of the corresponding isomeric species **20** (see species **8** and **9**). Contrary to this hypothesis, however, no useful level of regioselectivity was observed in entries 6, 7, and 10 (Table 1), regardless of the leaving group, solvent polarity, and the base employed for the elimination reactions. It is quite evident that either (i) the electronic and electrostatic effects favoring the formation of **4** were counterbalanced by other factors, such as the *syn*-directing effect of the lactone enolate, which might facilitate deprotonation at the nearest C-H proton through chelation of the metal ion, or (ii) resonance delocalization of the negative charge on the lactone oxygen effectively decreased the electron density at the methine of the enolate, thus reducing either the repulsive or the *syn*-directing effect of the carbanion. Equally unsatisfactory was the regiochemical outcome of elimination reactions carried out under normal E2 (entries 1, 2, 5, and 9 in Table 1) and E1 (entries 4 and 8) or Ei conditions (entry 11).

† Dedicated to Prof. P. A. Grieco, Indiana University, on the happy occasion of his half-century birthday.

(1) For leading references on synthetic achievements in this field, see the following references. PGA's: (a) Grieco, P. A; Abood, N. *J. Chem. Soc., Chem. Commun.* **1990**, 410 and ref 4 cited therein. Preclavulone A: (b) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1988**, *29*, 935. Methyl *epi*-jasmonate: (c) Tanaka, M.; Torii, S. *J. Org. Chem.* **1975**, *40*, 462. Seto, H.; Yoshioka, H. *Chem. Lett.* **1990**, 1797. Helmchen, G.; Goeke, A.; Lauer, G.; Urmann, M.; Fries, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1024. Kitahara, T.; Nishi, T.; Mori, K. *Tetrahedron* **1991**, *47*, 6999. Kitahara, T.; Warita, Y.; Abe, M.; Seya, M.; Takagi, Y.; Mori, K. *Agric. Biol. Chem.* **1991**, *55*, 1013. Reference 2b.

(2) Previous syntheses of 12-oxophytodienoic acid derivatives: (a) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008. (b) Crombie, L.; Mistry, K. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1981.

(3) Garlaschelli, L.; Vidari, G.; Zanoni, G. *Tetrahedron* **1992**, *48*, 9495.

(4) (a) Semiempirical MO calculations were performed with MNDO, AM1, and PM3 methods as implemented in the HYPERCHEM package of programs. (b) This result stands in striking contrast with the claim by Cook et al. (*J. Org. Chem.* **1988**, *53*, 2327) who found that the difference between the heats of formation of the *syn* and *anti* dienolate anions from **3** is rather small (1.8 kcal mol^{-1}). In our hands, the *anti* dianion from **3** was found to be more stable by 4–5 kcal mol^{-1} than its *syn* counterpart. (c) It is quite evident that the energy difference between **8** and **9** should be reduced in the presence of a solvent; however, this difference was considered large enough to guarantee the specific formation of dianion **8**.

(5) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55.

(6) Chamberlin, A. R.; Bloom, S. H. Lithioalkanes from Arenesulfonylhydrazones. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, U.K., 1990; Vol. 39, pp 1–83.

(7) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(8) Stemke, J. E.; Bond, F. T. *Tetrahedron Lett.* **1975**, 1815.

(9) **13** to **14**: $MsCl/Et_3N/CH_2Cl_2$, 97%; **13** to **15**: $TsCl/py/CH_2Cl_2$, 70%. **13** to **16**: $CCl_4/PPh_3/CH_2Cl_2$, 70%. **13** to **17**: $Tf_2O/py/CH_2Cl_2$, quantitative. **13** to **18**: Im_2CS/DMAP (cat)/toluene.

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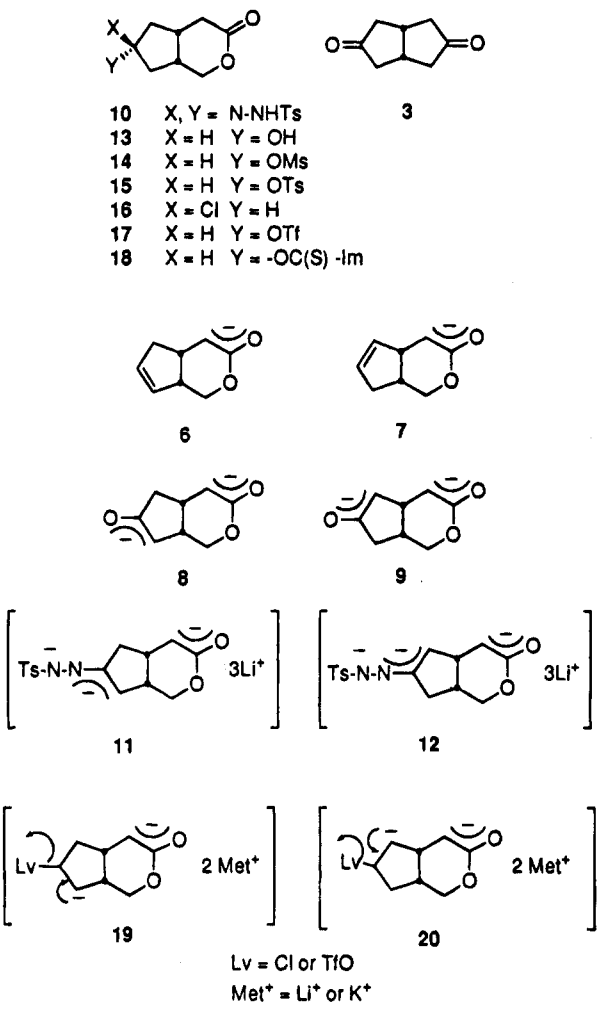
Table 1. Olefin Composition[a] for Various Elimination Reactions of Compounds 14–18

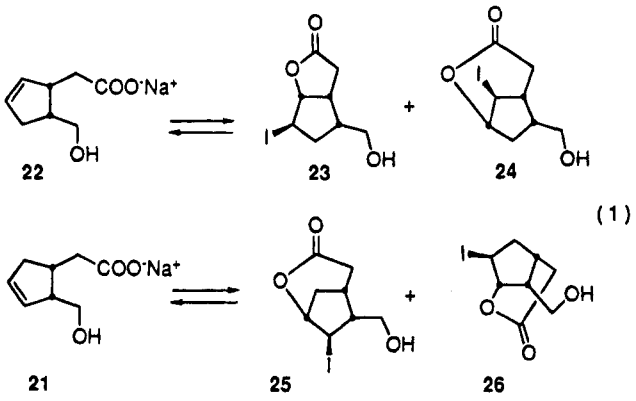
entry	starting material	reaction conditions	yield	4:5 ratio
1	14	DBU (2 equiv)/toluene/reflux/3.5 h	85	1:1.05
2	14	K_2CO_3 (10 equiv)/DMF/18-crown-6/reflux/4 h	60	1:1.3
3	14	LDA (2.5 equiv)/THF/−78 → 22 °C	*b*	
4	14	CF_3COOH/60 °C/72 h	55[c]	1:2
5	15	DBU (2 equiv)/toluene/reflux/4 h	70	1:1.1
6	16	$(C_6H_{11})_2NLi$ (3 equiv)/THF/22 °C	50[d]	1:1.2
7	16	$(C_6H_{11})_2NLi$ (3 equiv)/THF−DMPU/22 °C	58[d]	1:1.3
8	17	CF_3CH_2OH/22 °C/12 h	50[e]	1:1.8
9	17	DBU (3 equiv)/CH_2Cl_2/reflux/12 h	71	1:1.1
10	17	$[(CH_3)_3Si]_2NK$ (2.5 equiv)/THF−DMPU/18-crown-6/−78 °C/3 h	48	1:2.4
11	18	toluene/reflux/12 h	35	1:1.8

[a] The 4:5 ratio was determined by integration of the ^1H NMR signals for the corresponding olefin protons. [b] No reaction took place. [c] Contaminated by ca. 20% of an isomeric olefin. [d] In mixture with recovered starting **16**. [e] Contaminated by the trifluoroethyl ether of **13**.



Entry 10 afforded the best ratio of olefins **4** and **5**, but in unacceptable yields. Therefore, our synthesis of lactone **1** was continued utilizing the mixture of chromatographically indistinguishable olefins **4** and **5** (ca. 1:1), which was obtained in satisfactory yields from alcohol **13** through methanesulfonate **14** (Table 1, entry 1). Moreover, we expected to separate the two olefins in the following synthetic step and to recycle the unwanted regioisomer.

Exposure of the above mixture of olefins **4** and **5** to NaOH in H_2O–EtOH (1:1, v/v) readily afforded the corresponding carboxylate salts **21** and **22**, which were immediately submitted to iodolactonization conditions.[10] We anticipated that the γ-lactone **23**, arising from the 4-ene carboxylic acid salt **22** through the predominant "exocyclic attack", would be largely favored, under either kinetic or thermodynamic control, with respect to the more strained bicyclo[3.2.1]lactones **25** and **26**, arising from cyclization of the 5,6-diene carboxylic acid salt **21** (eq 1).[10] Indeed, exposure of a mixture of **21** and **22** to I_2



(0.5 equiv) in H_2O–THF–CH_2Cl_2 afforded iodolactone **23** in ca. 95% overall yield from **5**, contaminated by 20–25% of an unidentified compound,[11] while after acidification of the reaction mixture, unreacted olefin **4** was recovered in a pure form.[12] To our satisfaction, under iodolactonization conditions which allowed for full thermodynamic control (I_2 (0.5 equiv); MeCN:MeOH, 9:1; 24 h), the side product of cyclization was produced in less than 10% yield, so that a simple crystallization of the crude iodolactone fraction furnished pure **23** in 80–85% yield (on starting **5**). Exposure of recovered **4** to catalytic $RhCl_3 \cdot 3H_2O$[13] in boiling EtOH gave a 1:1.1 equilibrium mixture with **5**, which was recycled, raising the overall yield of **23** to 40–45% (from alcohol **13**). Conversion of iodolactone **23** to unsaturated lactone **1** proceeded uneventfully[14] through standard reactions (according to

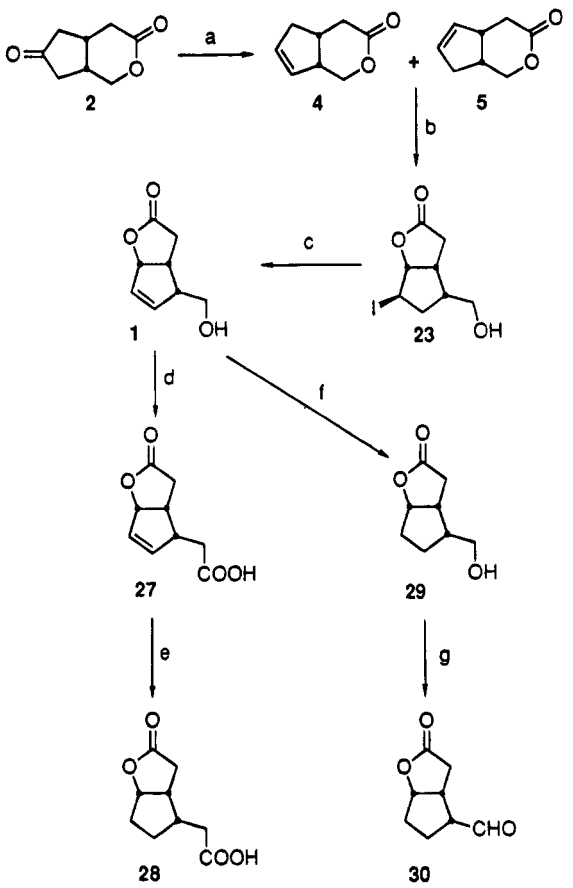
(10) (a) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (c) Harding, K. E.; Tiner, T. M. Electrophylic Heteroatom Cyclizations. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 363–421. (d) Mulzer, J. Halolactonization: The Career of a Reaction. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K., Reissig, H.-U., Eds.; VCH: Weinheim, 1991; pp 158–164.

(11) This compound is different from the products arising from the iodocyclization of isomerically pure olefin **4** in a separate experiment.

(12) The previous expeditious use of iodolactonization, as the preferred method of ene acid isomers separation, appears to be limited to simpler cases, such as the separation of straight chain α,β- and β,γ-unsaturated carbocyclic acids, or *endo–exo* norbornene carboxylic acids.[10a]

(13) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

Scheme 1



[a] Reagents: (a) (i) $NaBH_4$, MeOH, −30 °C, 3 h (97%), de 90%; (ii) MsCl, Et_3N, CH_2Cl_2 −20 °C, 15 min (96%); (iii) DBU, toluene, reflux, 5 h (85%); (b) (i) NaOH, H_2O:EtOH (1:1), 80 °C, 12 h; (ii) I_2 (0.5 equiv), MeOH:MeCN (1:9), 22 °C, 24 h (85% from **5**); (c) (i) Ac_2O:py (1:1), 22 °C, 3 h (100%); (ii) DBU, toluene, reflux, 3.5 h; (iii) K_2CO_3, MeOH, 22 °C, 1.5 h (87% for the two steps); (d) (i) MsCl, Et_3N, CH_2Cl_2, −20 °C, 15 min (98%); (ii) KCN, 18-crown-6, MeCN, reflux, 3 h (85%); (iii) NOVO nitrilase, phosphate buffer (pH 7.0), 27 °C, 3 d, then 3 N HCl (86%); (e) 5% Rh−Al_2O_3 catalyst, DME, H_2 (1 atm), 22 °C, 24 h (84%); (f) 5% Rh−AlO_3 catalyst, EtOAc, H_2 (1 atm), 22 °C, 12 h (99%); (g) 1.5 equiv of Dess−Martin periodinane, CH_2Cl_2, 22 °C, 1 h (91%).

Scheme 1), in 87% overall yield . The structure and stereochemistry of **1**[15] was fully supported by NMR spectra, NOE experiments,[16] and conversion to homologous acids **27** and **28** (Scheme 1), which are the key intermediates for the synthesis of 12-oxophytodienoic acid derivatives.[2b,17]

Smooth hydrogenation of **1** with 5% Rh−Al_2O_3 as catalyst gave the known alcohol **29**[18] in quantitative yield. The synthetic utility of synthon **1** was further demonstrated by the Dess−Martin[19] oxidation of **29** to aldehyde **30**, which is an attractive precursor of 11-deoxy-12-*epi*-prostaglandins. The ^1H NMR of **30** indicated less than 3% of the *exo* epimer.

Conversion of the readily available lactone **1** to other important biologically active cyclopentanoids is currently being investigated in our laboratory and will be reported in due course.

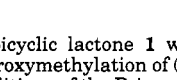
Experimental Section

Melting points were determined on a Fisher-Johns hot plate and are uncorrected. Elemental analyses were performed by the Analytical Laboratory of the Department of Organic Chemistry, University of Pavia. GLC was carried out on a 25 m cross-linked 5% phenylmethylsilicone HP-5 capillary column. IR spectra were recorded either neat or as a Nujol dispersion on NaCl plates. Data are reported in wavenumbers (cm^{-1}). ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were measured with $CDCl_3$ as the solvent and TMS as the internal standard (chemical shifts δ (ppm) and coupling constants J (Hz)). The number of hydrogens (in parentheses) attached to each carbon atom was determined by DEPT experiments. The EIMS spectra were recorded at 70 eV with a DIS system. All nonaqueous reactions were performed under an atmosphere of argon. Thin-layer chromatography (TLC) was carried out on 0.25 mm glass-supported silica gel plates, and visualization was effected with short-wavelength UV light (254 nm) or with 0.5% vanillin solution in H_2SO_4−EtOH (4:1), followed by heating. Flash column chromatography[20] was performed with silica gel (0.040−0.063 mm). Compounds were named following IUPAC rules as applied by AUTONOM, a personal computer software for systematic names in organic chemistry, Beilstein Institute and Springer Verlag. All commercial reagent grade solvents were dried and degassed by standard techniques just before use. NOVO nitrilase SP 409 was obtained from Dr. Norbert Klempier, Institute of Organic Chemistry, Graz University of Technology.

(4a*R,6*R**,7a*R**)-6-Hydroxy-4,4a,5,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyran-3-one (13).** Solid $NaBH_4$ (0.55 g, 14.5 mmol) was added portionwise to a solution of lactone **2** (4.5 g, 29 mmol) in MeOH (250 mL) at −30 °C, and the resulting mixture was stirred at −30 °C for 3 h. After the reaction was quenched with Me_2CO, evaporation of the solvent gave a jelly residue which was passed through Celite (CH_2Cl_2) to remove boron salts. Elimination of the solvent gave **2** (4.4 g, 97%) as an oil contaminated by 5% of the *exo* isomer (GLC): IR (neat) 3410, 1740, 1430, 1390, 1345, 1260, 1080, 1035, 970, 820 cm^{-1}; ^1H NMR δ 1.47−1.59 (2H, m), 1.78 (1H, bs, OH), 2.0−2.18 (2H, m), 2.45−2.65 (4H, m), 4.19−4.40 (3H, m); ^{13}C NMR δ 32.7 (1), 35.1 (1), 35.2 (2), 37.3 (2), 41.6 (2), 70.1 (2), 73.3 (1), 174.0 (0); MS m/z (relative intensity) 156 (M, 25), 138 (28), 110 (32), 97 (83), 84 (53), 73 (100), 69 (80), 55 (69), 45 (78). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.58; H, 7.70.

(4a*R,6*R**,7a*R**)-6-(Methanesulfonyloxy)-4,4a,5,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyran-3-one (14).** A stirred solution of alcohol **13** (0.156 g, 1 mmol) in dry CH_2Cl_2 (5 mL) was cooled to −20 °C and treated with dry Et_3N (0.210 mL, 1.5 mmol) and then with freshly distilled methanesulfonyl chloride (0.086 mL, 1.1 mmol). After the addition was complete, the solution was stirred for 15 min at −20 °C and then concentrated in vacuo. The residue was slurried for 10 min in EtOAc (50 mL), and the solution was decanted away from the insoluble material. The EtOAc slurry and the decantation were repeated twice. The combined EtOAc washings were filtered through Celite and concentrated in vacuo to yield a sticky oil, which slowly crystallized upon Et_2O being added and the solution being cooled to −20 °C to give the desired methanesulfonate **14** (225 mg, 96% yield). An analytical sample was prepared by crystallization

(14) Acetylation of the hydroxymethyl group of **23** was necessary to avoid formation of epoxide (**i**) in the dehydroiodination step.



(i)

(15) Previously, the bicyclic lactone **1** was obtained as a minor product of the allylic hydroxymethylation of (±)-2-oxabicyclo[3.3.0]oct-7-en-3-one under the conditions of the Prins reaction (*exo*:*endo* isomers, 8:1). However, neither has this compound been fully characterized spectroscopically nor has its synthetic value been recognized so far (Tolstikov, G. A.; Miftakhov, M. S.; Akhmetvaleev, R. R.; Balezina, G. G.; Valeev, F. A. *Zh. Org. Khim.* **1989**, *25*, 1567).

(16) NOE was observed at H-5 (4%), H-6 (1%), and H-8 (4%) upon irradiation of H-1.

(17) The reported literature value for the mp of lactone **27** is 68−69 °C, which must be revised as 104−106 °C (Prof. L. Crombie, private communication).

(18) Dyadchenko, M. A.; Danilova, G. A.; Spanig, I.; Schick, G.; Pivnitskii, K. K.; *Zh. Org. Khim.* **1990**, *26*, 2536.

(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

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

from toluene: mp 84–85 °C; IR (Nujol dispersion) 1734, 1243, 1172, 1082, 1034, 970, 896, 860 cm^{-1}; ^1H NMR δ 1.78–1.97 (2H, m), 2.22–2.38 (2H, m), 2.47–2.57 (1H, m), 2.58–2.75 (3H, m), 3.04 (3H, s), 4.19 (1H, dd, J = 12.0 and 7.0), 4.33 (1H, dd, J = 12.0 and 5.0), 5.10 (1H, qu, J = 5.5); ^{13}C NMR δ 32.1 (1), 34.3 (1), 34.3 (2), 35.2 (2), 38.4 (3), 39.3 (2), 69.1 (2), 81.4 (1), 172.6 (0); MS (CI, CH_4) m/z 235 (M + H).

(4a*R,7a*S**)-4,4a,5,7a-Tetrahydro-1*H*-cyclopenta[*c*]pyran-3-one (4) and (4a*R**,7a*S**)-4,4a,7,7a-Tetrahydro-1*H*-cyclopenta[*c*]pyran-3-one (5).** DBU (0.824 mL, 5.51 mmmol) was added dropwise to a solution of methanesulfonate **14** (0.65 g, 2.78 mmol) in dry toluene (10 mL), and the mixture was heated at reflux for 5 h. After being cooled, the mixture was diluted with toluene and washed with 1 N HCl. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo gave a residue which was purified by silica gel flash chromatography (hexane:EtOAc, 7:3) to afford 0.326 g (85%) of a chromatographically inseparable 1:1 mixture of olefins **4** and **5** as a colorless solid: mp 35–36 °C; IR (neat) 3058, 2915, 1745, 1479, 1431, 1384, 1266, 1235, 1137, 1080, 990 cm^{-1}; ^1H NMR δ 2.10–2.45 (2H, m), 2.57–2.85 (2.5H, m), 2.85–3.0 (0.5H, m), 3.17–3.27 (0.5H, m), 3.25–3.4 (0.5H, m), 4.0 (0.5H, dd, J = 11.5 and 6.5), 4.08 (0.5H, dd, J = 11.5 and 5.5), 4.24 (0.5H, dd, J = 11.5 and 4.5), 4.30 (0.5H, dd, J = 11.5 and 4.5), 5.45 (0.5H, m), 5.51, (0.5H, m), 5.70 (0.5H, m), 5.80 (0.5H, m); ^{13}C NMR δ 31.6 (1), 33.7 (2), 33.8 (1), 35.4 (2), 36.1 (2), 40.3 (2), 41.8 (1), 44.6 (1), 69.0 (2), 70.2 (2), 128.7 (1), 130.8 (1), 131.7 (1), 132.8 (1), 173.1 (0), 173.3 (0); MS m/z (relative intensity) 138 (M, 1.5), 96 (17), 79 (63), 66 (100), 60 (54), 51 (18). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.51; H, 7.36.

Acetic Acid (3a*R,4*R**,6*R**,6a*R**)-6-Iodo-2-oxohexahydrocyclopenta[*b*]furan-4-yl Methyl Ester (23).** Solid NaOH (0.63 g, 15.7 mmol) was added to a suspension of a 1:1 mixture of olefins **4** and **5** (2.17 g, 15.7 mmmol) in 1:1 H_2O:EtOH (5 mL), and the mixture was heated at 80 °C overnight. The solution was taken to dryness to give a residue which was washed with CH_2Cl_2 (2 × 5 mL) and decanted to afford the sodium salts **21** and **22** (2.7 g, >99%) as a white solid. I_2 (317 mg, 1.25 mmol) was added to a solution of **21** and **22** (445 mg, 2.5 mmol) in MeOH (5 mL) and MeCN (45 mL) and cooled to 0 °C. The mixture was stirred at room temperature for 24 h in the dark, then excess I_2 was destroyed by addition of saturated aqueous Na_2SO_3 solution, and the volatiles were removed in vacuo under 30 °C. The residue was taken up in H_2O (15 mL) and CH_2Cl_2 (15 mL) under vigorous stirring. The two phases (A and B) were separated. The aqueous layer A was acidified with 1 N HCl to pH 2, stirred overnight, and extracted with CH_2Cl_2 (3 × 15 mL). The CH_2Cl_2 layer was washed with brine, dried ($MgSO_4$), and taken to dryness to give isomerically pure olefin **4** (138 mg, 80% recovery from starting olefin). **4**: ^1H NMR δ 2.1 (1H, m), 2.31 (1H, dd, J = 15.0 and 5.5), 2.59 (1H, dd, J = 15.0 and 7.0), 2.72 (1H, ddq, J = 17.5, 9.5, and 2.2), 2.87 (1H, m), 3.16 (1 H, m), 4.08 (1H, dd, J = 11.5 and 5.0), 4.30 (1H, dd, J = 11.5 and 4.5), 5.42 (1H, dq, J = 6.0 and 2.5), 5.76 (1H, dq, J = 6.0 and 2.2); ^{13}C NMR δ 31.6 (1), 35.4 (2), 40.3 (2), 44.6 (1), 69.0 (2), 128.7 (1), 132.8 (1), 173.1 (0).

Phase B was washed with brine, dried ($MgSO_4$), and taken to dryness. The residue (0.33 g) was crystallized from Et_2O–hexane to afford pure **23** (0.298 g, 85% from **5**): mp 96–98 °C; IR (Nujol dispersion) 3260, 2929, 1784, 1460, 1376, 1166, 1039, 1020, 995, 886 cm^{-1}; ^1H NMR δ 1.9–2.03 (1H, ddd, J = 15.0, 12, and 5.0), 2.09 (1H, dd, J = 15.0 and 6.5), 2.7 (1H, dd, J = 19.0 and 9.5), 2.76 (1H, dd, J = 19.0 and 3.5), 2.92 (1H, m), 3.27 (1H, tdd, J = 9.5, 6.0, and 3.5), 3.72 (1H, dd, J = 11.0 and 8.0), 3.85 (1H, dd, J = 11.0 and 5.0), 4.52 (1H, d, J = 5.0), 5.2 (1H, d, J = 6.0); ^{13}C NMR δ 27.6 (1), 29.7 (2), 37.4 (2), 38.1 (1), 41.5 (1), 61.3 (2), 92.4 (1), 176.9 (0); MS (CI, CH_4) m/z 283 (M + H), 265 (M + H − H_2O), 155 (M − I), 137 (M − I − H_2O).

(3a*R,4*R**,6a*S**)-4-(Hydroxymethyl)-3,3a,4,6a-tetrahydrocyclopenta[*b*]furan-2-one (1).** Iodolactone **23** (0.148 g, 0.52 mmol) was acetylated with dry Ac_2O (0.25 mL) and pyridine (0.25 mL) in the standard way. Removal of the volatiles gave an oily residue which was immediately dissolved in dry toluene (10 mL) to which freshly distilled (CaH_2) DBU (0.27 mL, 1.8 mmol) was added. The solution was heated at reflux for 3.5 h, cooled to room temperature, and taken to dryness. The oily residue was dissolved in MeOH (4 mL), and solid K_2CO_3 (0.15 g) was added. The mixture was stirred for 1.5 h at room temperature, and then MeOH was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with 0.1 N HCl (5 mL) and brine, dried ($MgSO_4$), and subjected to flash chromatography (silica gel, hexane:EtOAc, 1:1) to give the enelactone **1** (70.3 mg, 87% from **23**): IR (neat) 3428, 3016, 2927, 1764, 1291, 1173, 1139, 1023, 973, 964, 759 cm^{-1}; ^1H NMR δ 2.15 (1H, broad, OH), 2.58–2.72 (2H, m), 3.07 (1H, ddd, J = 8.5, 6.5, and 4.8), 3.24 (1H, dddd, J = 9.5, 8.5, 7.5, and 6.5), 3.67 (1H, dd, J = 11.0 and 6.5), 3.77 (1H, dd, J = 11.0 and 4.8), 5.46 (1H, dd, J = 7.5 and 1.5), 6.15 (2H, bs); ^{13}C NMR δ 29.7 (2), 37.8 (1), 48.9 (1), 61.7 (2), 88.6 (1), 130.3 (1), 137.9 (1), 177.4 (0); MS (CI, CH_4) 155 (M + H), 137 (M + H − H_2O), 125 (M + H − CH_2O); MS (CI, NH_3) m/z 189 (M + NH_3 + NH_4), 172 (M + NH_4). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.30; H, 6.58.

(3a*R,4*R**,6a*R**)-(2-Oxo-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-yl)acetic Acid (27).** Dry Et_3N (0.130 mL, 0.93 mmol) and then MsCl (0.050 mL, 0.65 mmol) were added dropwise to a solution of **1** (91 mg, 0.58 mmol) in dry CH_2Cl_2 (3 mL) cooled to −20 °C. After being stirred for 15 min, the solution was taken to dryness and the solid residue suspended in EtOAc and filtered off. The EtOAc solution was evaporated in vacuo and the residue separated on a short flash chromatography column (silica gel, EtOAc:hexane, 3:2) to afford 132 mg (98%) of the expected methanesulfonate of alcohol **1**: mp 89–91 °C; IR (Nujol dispersion) 3019, 1752, 1618, 1460, 1339, 1190, 1164, 1027, 1006, 973, 954, 941, 835, 780, 748, 721 cm^{-1}; ^1H NMR δ 2.48 (1H, dd, J = 18.5 and 6.0), 2.64 (1H, dd, J = 18.5 and 10), 3.05 (3H, s), 3.2–3.4 (2H, m), 4.25 (1H, dd, J = 10.5 and 6.5), 4.32 (1H, dd, J = 10.5 and 5.0), 5.48 (1H, bd, J = 6.5), 5.98 (1H, dd, J = 5.5 and 1.5), 6.05 (1H, dt, J = 5.5 and 2.0); MS (CI, NH_3) m/z 267 (M + NH_4 + NH_3), 250 (M + NH_4). This methanesulfonate (40 mg, 0.172 mmol) was added to a stirred solution of KCN (24 mg, 0.36 mmol) and 18-crown-6 (5 mg, 0.019 mmol) in acetonitrile (2.5 mL). The mixture was heated at reflux for 3 h, cooled to room temperature, and filtered. The filtrate was taken to dryness to give a residue which was purified by flash chromatography (silica gel, hexane:EtOAc, 3:2), affording 23.8 mg (85%) of the expected nitrile: IR (neat) 2963, 2248, 1763, 1425, 1365, 1330, 1172, 1020, 785 cm^{-1}; ^1H NMR δ 2.32 (1H, dd, J = 18.0 and 7.5), 2.34 (1H, dd, J = 17.0 and 8.5), 2.47 (1H, dd, J = 17.0 and 7.5), 2.61 (1H, dd, J = 18.0 and 10), 3.23 (1H, qq, J = 7.5 and 2.0), 3.33 (1H, dq, J = 10.0 and 7.5), 5.45 (1H, dq, J = 7.5 and 1.5), 5.92 (1H, dt, J = 6.0 and 1.4), 5.97 (1H, dt, J = 6.0 and 2.0); MS (CI, CH_4) m/z 164 (M + H); EIMS m/z (relative intensity) 163 (M, 1.5), 79 (100), 77 (25). The above nitrile (20 mg, 0.123 mmol) was suspended in a 0.1 M phosphate buffer (2 mL, pH 7), and 100 mg of immobilized NOVO nitrilase was added in one portion. The mixture was vigorously stirred for 3 d at 27 °C, during which time conversion of nitrile first to the corresponding amide and then to acid **27** was monitored by TLC. When conversion to acid **27** was complete, the pH was adjusted to 1 with 3 N HCl and the suspension centrifuged. The supernatant solution was diluted with H_2O (10 mL), saturated with NaCl, and extracted with EtOAc (8 × 10 mL), while the centrifuged residue was suspended in MeOH (5 mL) and filtered off. The combined organic layers were evaporated in vacuo at room temperature to afford a residue which was crystallized from CH_2Cl_2–hexane to give pure **27**[2b] (19.2 mg, 86%): mp 105–106 °C;[2b,17] IR (KBr) 3450, 2925, 1720, 1412, 1365, 1263, 1187, 1024, 1005, 952 cm^{-1}; ^1H NMR δ 2.37 (1H, dd, J = 18.0 and 8.0), 2.46 (1H, dd, J = 16.5 and 8.5), 2.56 (1H, dd, J = 18.0 and 10.0), 2.61 (1H, dd, J = 16.5 and 7.0), 3.33 (1H, m), 3.39 (1H, dq, J = 10.0 and 7.5), 5.52 (1H, dq, J = 7.5 and 1.5), 5.92 (1H, dt, J = 6.0 and 2.0), 5.97 (1H, dt, J = 6.0 and 1.2), 8.5 (1H, broad, OH); ^{13}C NMR δ 29.4 (2), 35.0 (2), 39.4 (1), 42.1 (1), 88.6 (1), 129.4 (1), 138.1 (1), 176.7 (0), 177.1 (0); EIMS m/z (relative intensity) 164 (M − H_2O, 20), 136 (100), 93 (48), 91 (58), 79 (24), 77 (31), 60(25); MS (CI, CH_4) m/z 183 (M + H), 165 (M + H − H_2O), 137.

(3a*R,4*S**,6a*S**)-(2-Oxohexahydrocyclopenta[*b*]furan-4-yl)acetic Acid (28).** Rh−Al_2O_3 (5%, 5 mg) was added to a stirred solution of acid **27** (40 mg, 0.22 mmol) in DME (2 mL). The mixture was hydrogenated at room temperature and atmospheric pressure for 24 h, and then the catalyst was filtered off and washed thoroughly with EtOAc. The combined organic

phases were evaporated in vacuo to afford a residue which was crystallized from Et_2O–hexane to give acid **28** (34 mg, 84%): mp 84–85 °C (lit.[2b] 86–87 °C); IR (KBr) 2925, 1760, 1695, 1455, 1410, 1310, 1200, 1085, 1025, 995, 940 cm^{-1}; ^1H NMR δ 1.3–1.45 (1H, m), 1.7–1.92 (2H, m), 2.08 (1H, dd, J = 13.0 and 7.0), 2.33–2.70 (5H, m), 3.14 (1H, m), 5.08 (1H, bt, J = 6.5); ^{13}C NMR δ 28.8 (2), 28.9 (2), 32.6 (2), 34.8 (2), 38.4 (1), 40.0 (1), 85.7 (1), 177.3 (0), 177.7 (0); MS m/z (relative intensity) 184 (M, 4), 166 (M − H_2O, 38), 138 (M − HCOOH, 35), 124 (M − CH_3COOH, 32), 96 (100), 80 (51), 60 (CH_3COOH, 35).

(3a*R,4*R**,6a*S**)-4-(Hydroxymethyl)hexahydrocyclopenta[*b*]furan-2-one (29).** Enelactone **1** (110 mg, 0.71 mmol) in EtOAc (3 mL) was hydrogenated for 12 h over 5% Rh–Al_2O_3 at 22 °C and atmospheric pressure. The suspension was diluted with EtOAc (5 mL) and the catalyst filtered off through a short pad of Celite. Evaporation of the solvent in vacuo afforded **29**[18] (110 mg, 98.7%) as a colorless oil: IR (neat) 3400, 1748, 1364, 1302, 1188, 1072, 1030, 998 cm^{-1}; ^1H NMR δ 1.25–1.46 (1H, m), 1.7–1.84 (2H, m), 2.08 (1H, bdd, J = 13.5 and 7.0), 2.12–2.30 (1H, m), 2.5–2.65 (2H, m), 2.90 (1H, broad, OH), 3.05 (1H, tt, J = 8.5 and 6.5), 3.59 (1H, dd, J = 11.0 and 8.5), 3.75 (1H, dd, J = 11.0 and 5.9), 5.05 (1H, m, J = 6.5, 4.5, and 1.5); ^{13}C NMR δ 25.6 (2), 29.1 (2), 32.4 (2), 39.2 (1), 44.0 (1), 62.1 (2), 86.5 (1), 178.6 (0); EIMS m/z (relative intensity) 156 (M, 1), 138 (M − H_2O, 5), 126 (M − CH_2O, 75), 110 (29), 108 (25), 97 (24), 81 (63), 67 (100); MS (CI, CH_4) m/z 157 (M + H), 139 (M + H − H_2O). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.48; H, 7.80.

(3a*R,4*R**,6a*S**)-2-Oxo-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-carbaldehyde (30).** Solid Dess–Martin periodinane[19] (522 mg, 1.23 mmol) was added to a stirred solution of **29** (128 mg, 0.82 mmol) in CH_2Cl_2 (5 mL). After 1 h, the suspension was diluted with 50 mL of Et_2O, and 2 mL of saturated aqueous $NaHCO_3$ and 1 mL of saturated aqueous Na_2SO_3 were added. The mixture was stirred until two clear layers were obtained. The ether layer was separated, washed with 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of H_2O, and dried ($MgSO_4$). Removal of the ether gave an oily residue (119 mg) which could not be chromatographed through silica gel without ready epimerization of the *endo* aldehyde group of compound **30**. The NMR spectra showed that crude **30**, thus obtained, was contaminated by less than 3% of the *exo* epimer: ^1H NMR δ 1.17–2.2 (4H, m), 2.40 (1H, dd, J = 18.5 and 5.2), 2.70 (1H, dd, J = 18.5 and 9.5), 2.9 (1H, m), 3.3 (1H, m), 5.10 (1H, m), 9.80 (1H, s); ^{13}C NMR δ 23.5 (2), 30.2 (2), 32.4 (2), 38.4 (1), 55.0 (1), 84.9 (1), 177.0 (0), 201.1 (1); MS (CI, CH_4) m/z 155 (M + H).

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