Tetrahedron Letters, Vol. 34, No. 15, pp. 2473-2476, 1993
Printed in Great Britain

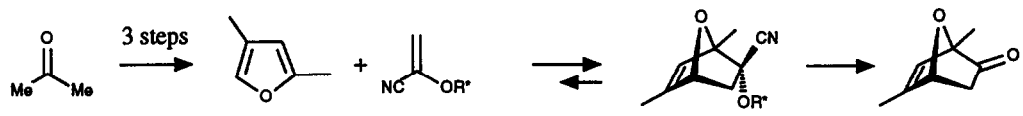
0040-4039/93 $6.00 + .00
Pergamon Press Ltd

TOTAL ASYMMETRIC SYNTHESIS OF POLYPROPIONATE FRAGMENTS AND DOUBLY BRANCHED HEPTONO-1,4-LACTONES

Philippe Kernen, and Pierre Vogel*
Section de chimie de l'Université de Lausanne, 2, rue de la Barre, CH 1005 Lausanne, Switzerland

Summary: *(+)-(1R,2S,4R)-2-Cyano-1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1'R)-camphanate ((+)-3) and (+)-(1R,4R)-1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one ((+)-4) were obtained readily from 2,4-dimethylfuran. (+)-3 was converted into 2,7-dideoxy-2,4-di-C-methyl-L-*glycero- *and D-*glycero-*L-*altro-*heptono-1,4-lactone ((+)-17) and ((+)-18).*

Many bioactive natural products contain polysubstituted carbon chains with methyl and hydroxyl groups (polypropionates and analogues).[1] Several ingenious asymmetric and stereoselective synthetic approaches to fragments of these systems carrying several consecutive chiral centres have been proposed.[2-4] Optically pure (+)- and (-)-7-oxabicyclo[2.2.1]hept-5-en-2-one and derivatives ("naked sugars"[5]) obtained via Diels-Alder addition of furan to optically pure 1-cyanovinyl esters are useful chirons that have been used to prepare all kinds of natural products and compounds of biological interest[6] including long chain carbohydrates[7] and their analogues[8], and C-linked disaccharides[9]. We have now found that 2,4-dimethylfuran (**1**) obtained in three steps from acetone[10] can be readily converted into optically pure 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives. These systems ("naked sugars of the second generation") can be converted into polypropionate fragments including 2,7-dideoxy-2,4-di-*C*-methyl-L-*glycero*- and D-*glycero*-L-*altro*-heptono-1,4-lactone ((+)-**17**) and ((+)-**18**).



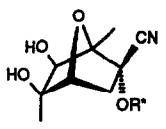
1 **2** (+)-**3** (+)-**4**

R*= (1R)-camphanoyl

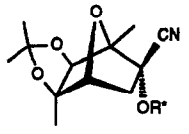
A 10:1:0.25 mixture of **1**, 1-cyanovinyl-(1'R)-camphanate[11] and ZnI_2 (20°C, 2 days) gave, after filtration on silica gel and two recrystallizations from EtOAc/hexane, the adduct (+)-**3** in 54% yield.[12a] Its diastereomeric purity was 99.75:0.25 (by 360 MHz ^{1}H-NMR using ^{13}C-H satellites) and the *endo* configuration of the camphanate moiety was confirmed by NOE measurements in the ^{1}H-NMR spectrum. Heating the mother liquors from the recrystallization of (+)-**3** to 120°C (toluene) allowed the recovery of unreacted **2** (30%). Alkaline hydrolysis (KOH 3N, 1:1 THF/H_2O, 20°C, 1h) followed by treatment with 40% aqueous H_2CO (25°C, 15 min.) gave enone (+)-**4** (81%). Its CD spectrum[12b] was similar to that of (+)-(1R,4R)-7-oxabicyclo[2.2.1]hept-5-en-2-one[11] which confirmed the (1R,4R) configuration.

Double hydroxylation of the double bond in (+)-**3** with N-methylmorpholine oxide monohydrate and 0.01 equivalent of OsO_4 in 8:1 acetone/H_2O (20°C, 3h) afforded diol (-)-**5** (85%) which was protected as the acetonide (-)-**6** (95%)[13a] by treatment with 2,2-dimethoxypropane in acetone containing a catalytical amount of *para*-toluenesulfonic acid. The *endo* configuration of H-C(6) was given by the observation of a NOE

between that proton and the camphanate protons. This was expected by analogy with other examples of double hydroxylations of 7-oxabicyclo[2.2.1]hept-2-ene systems.[6,14] Methanolysis of (-)-**6** (MeOH, K_2CO_3, 20°C, 45 min.), followed by treatment with formaline led to ketone (+)-**7** (99%)[13b] and the recovery of (-)-(1R)-camphanic acid (91%), the chiral auxiliary used to generate the starting dienophile **2**.[11] The Baeyer-Villiger oxidation of (+)-**7** with *meta*-chloroperbenzoic acid (CH_2Cl_2, $NaHCO_3$, 20°C, 5h) afforded lactone (-)-**8** (92%) with high regioselectivity.[15,16]

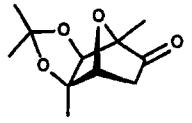


(-)-**5**

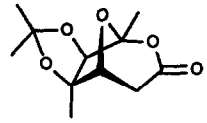


(-)-**6**

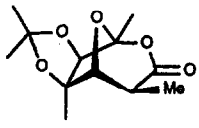
R*=(1R)-camphanoyl



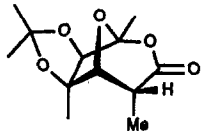
(+)-**7**



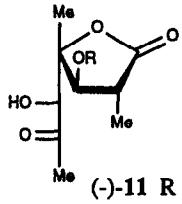
(-)-**8**



(-)-**9**

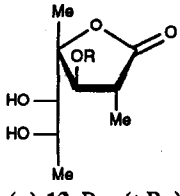


(-)-**10**



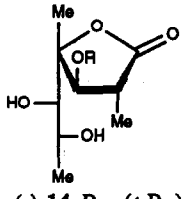
(-)-**11** R = H

(-)-**12** R = (*t*-Bu)Me_2Si



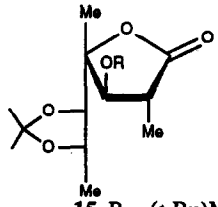
(+)-**13** R = (*t*-Bu)Me_2Si

(+)-**17** R = H

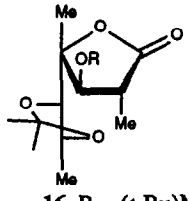


(-)-**14** R = (*t*-Bu)Me_2Si

(+)-**18** R = H



15 R = (*t*-Bu)Me_2Si



16 R = (*t*-Bu)Me_2Si

Deprotonation of uronolactone (-)-**8** with $(Me_3Si)_2NLi$ (1.0 equivalent) in THF (-65°C) followed by addition of MeI (-65°C to -20°C) yielded the *exo*-α-methyllactone (-)-**9** (92%).[17a] The isomeric *endo*-α-methyllactone (-)-**10** was not visible in the 250 MHz ^{1}H-NMR spectrum of the crude reaction mixture. Treatment of (-)-**9** with $(Me_3Si)_2NLi$ (1.2 equivalent) in THF at -50°C followed by quenching of the enolate with MeOH led to a 88:12 mixture of (-)-**10** and (-)-**9** from which pure (-)-**10** (77%)[17b] could be isolated by flash chromatography and recrystallization. Acidic hydrolysis of (-)-**10** (1N HCl, 60°C, 24h) gave the crystalline dihydroxy-γ-lactone (-)-**11**, which was partially protected by silylation with (*t*-Bu)$Me_2SiOSO_2CF_3$ and 2,6-lutidine (CH_2Cl_2, 0°C, 30 min.) affording (-)-**12** (82%).[18] Reduction of ketone (-)-**12** with $NaBH_4$ (MeOH, -78°C) led to a 1:1 mixture of diols (+)-**13** (49%) and (-)-**14** (44%) which were separated by flash chromatography on silica gel. Reduction of (-)-**12** with L-Selectride (Li(*i*-Bu)$_3$BH) in THF at -78°C gave a 9:1 mixture of (+)-**13** and (-)-**14**, the structures of which were established by the 360 MHz ^{1}H-NMR spectra of the corresponding acetonides **15** and **16** obtained by treatment with 2,2-dimethoxypropane and a trace amount of *para*-toluenesulfonic acid (20°C, 3 days). While there was a significant NOE between H-C(5) and H-C(6) in the L-*glycero*-L-*altro*-heptono-1,4-lactone derivative **15**, no NOE was observed between these protons in the D-*glycero*- isomer **16**.

Unprotected heptono-1,4-lactones (+)-**17** (95%) and (+)-**18** (96%)[19,20] were obtained by treatment of (+)-**13** and (-)-**14**, respectively, with 40% HF.

This work demonstrates the possibility to transform acetone into a new kind of optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives that can be converted with high stereoselectivity into potentially useful polypropionate fragments and doubly branched heptose derivatives.

Acknowledgements. We are grateful to the *Swiss National Science Foundation*, the *Fonds Herbette* (Lausanne) and *Hoffmann-La-Roche & Co.*,AG (Basel) for financial support.

REFERENCES AND FOOTNOTES

1. See e.g.: Higton, A. A.; Roberts, A. D., *"Dictionary of Antibiotics and Related Substances"*, Bycroft, B. W.,Ed., Chapmann & Hall, London, **1988**; Masamune, S.; McCarthy, P.A., *"Macrolide Antibiotics. Chemistry, Biology, and Practice"*, Omura, S., Ed., Academic Press, Orlando, **1984**.
2. See e.g.: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569; Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 489; Mulzer, J. *Ibid.* **1991**, *30*, 1452.
3. For recent examples, see: Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233 and ref. cited therein; Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127 and ref. cited therein; Harada, T.; Kagamihara, Y.; Tanaka, S.; Sakamoto, K.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1637; Hale, M. R.; Hoveyda, A. H. *Ibid.* **1992**, *57*, 1643; Schlessinger, R. H.; Mjalli, A. M. M.; Adams, A. D.; Springer, J. P.; Hoogsteen, K. *Ibid.* **1992**, *57*, 2992; Myles, D. C.; Danishefsky, S. J.; Schulte, G. *Ibid.* **1990**, *55*, 1636; Horita, K.; Tanaka, K.; Inoue, T.; Yonemitsu, O. *Tetrahedron Lett.* **1992**, *33*, 5541; Kim, Y. G.; Whang, K.; Cooke, R. J.; Cha, J. K. *Ibid.* **1990**, *31*, 3275; Roush, W. R.; Palkowitz, A. D. *J. Org. Chem.* **1989**, *54*, 3009; Smith, A. B.; Hale, K. J. *Tetrahedron Lett.* **1989**, *30*, 1037; Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247; Martin, S. F.; Pacofsky, G. J.; Gist, R. P.; Lee, W.-C. *Ibid.* **1989**, *111*, 7634; Murphy, P. J.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1059; Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1990**, *55*, 1540; **1991**, *56*, 2225; Ziegler, F. E.; Becker, M. R. *Ibid.* **1990**, *55*, 2800; Evans, D. A.; Sheppard, G. S. *Ibid.* **1990**, *55*, 5192; Born, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 2242; Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866; Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *Ibid.* **1990**, *112*, 5290; Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *Ibid.* **1990**, *112*, 5583; Roush, W. R.; Palkowitz, A. D.; Ando, K. *Ibid.* **1990**, *112*, 6348.
4. Polypropionates synthesis using dideoxy-di-C-methyl carbohydrates: see e.g.: Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170; Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119; Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *Ibid.* **1989**, *111*, 2967; Nakata, M.; Akiyama, N.; Kamata, J.-I.; Kojima, K.; Masuda, U.;Kinashita, M.; Tatsuta, K. *Tetrahedron* **1990**, *46*, 4629; Sviridov, A. F.; Borodkin, V. S.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Ibid.* **1991**, *47*, 2291; **1991**, *47*, 2317; Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron Lett.* **1992**, *33*, 5537; Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276; Nakata, M.; Ikeyama, Y.; Takao, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3252; Nakata, M.; Toshima, K.; Kai, T.; Kinoshita, M. *Ibid.* **1985**, *58*, 3457; Tarara, G.; Hoppe, D. *Synthesis* **1989**, 89; Hoppe, D.; Tarara, G.; Wilckens, M. *Ibid.* **1989**, 83.
5. Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348; Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729; see also: Saf, R.; Faber, K.; Penn, G.; Griengl, H. *Tetrahedron* **1988**, *44*, 389; Ronan, B.; Kagan, H. B. *Tetrahedron: Asymmetry* **1991**, *2*, 75.
6. Vogel, P.; Fattori, D; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173; Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10587; de Guchteneere, E.; Fattori, D.; Vogel, P. *Ibid.* **1992**, *48*, 10603; Jeanneret, V.; Gasparini, F.; Péchy, P.; Vogel, P. *Ibid.* **1992**, *48*, 10637; Moritz, V.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 5243.
7. Jeganathan, S.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 1133.
8. Reymond, J.-L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128; Chen, Y.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 4917.
9. Bimwala, R. M.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076.
10. Morel, T.; Verkade, P. E. *Rec. Trav. Chim. Pays-Bas* **1949**, *68*, 619; **1951**, *70*, 35.
11. Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865.

12. a) Data of (+)-**3**: m.p. 136°C, $[\alpha]^{25}_{589}$ = +92 (c = 1.0, $CHCl_3$); b) data of (+)-**4**: b.p. 35°C, 1Torr; $[\alpha]^{25}_{589}$ = +306 (c = 1.0, $CHCl_3$); IR (film) ν: 2980, 2940, 1750, 1630, 1440 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 5.64 (qd, ^4J = 1.8, ^5J = 0.5, H-C(6)); 4.85 (d, ^3J = 4.3, H-C(4)); 2.25 (ddd, ^2J = 15.9, ^3J = 4.3, ^5J = 0.6, H_{exo}-C(3)); 1.88 (d, ^2J = 15.9, H_{endo}-C(3)); 1.85 (d, ^4J = 1.8, Me-C(5)); 1.42 (s, Me-C(1)); CD (c = 2.1 mg/ml, EtOH 95%, 25°C): $\Delta\varepsilon_{308}$ = +2.4, $\Delta\varepsilon_{252}$ = +0.03, $\Delta\varepsilon_{224}$ = +1.2, $\Delta\varepsilon_{207}$ = 0; UV (EtOH 95%): λ_{max} = 211 nm (ε = 3310), 307 (ε = 240).
13. a) Data of (-)-**6**: m.p. 159°C, $[\alpha]^{25}_{589}$ = -42 (c = 1.0, $CHCl_3$); IR (KBr) ν: 2990, 2950, 2880, 1800, 1765, 1470 cm^{-1}; b) data of (+)-**7**: m.p. 48°C, $[\alpha]^{25}_{589}$ = +60 (c = 1.0, $CHCl_3$); IR (KBr) ν: 2990, 2940, 1765, 1380 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.48 (d, ^3J = 6.2, H-C(4)); 3.82 (s, H-C(6)); 2.48 (dd, ^2J = 17.9, ^3J = 6.2, H_{exo}-C(3)); 2.14 (d, ^2J = 17.9, H_{endo}-C(3)); 1.51, 1.45, 1.43, 1.36 (4s, 4Me).
14. Schmidt, R. R.; Beitzke, C.; Forrest, A. K. *J. Chem. Soc., Chem. Commun.* **1982**, 909; Wagner, J.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1988**, *71*, 624.
15. Arvai, G.; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10621.
16. Data of (-)-**8**: m.p. 51-52°C, $[\alpha]^{25}_{589}$ = -87 (c = 1.0, $CHCl_3$); IR (KBr) ν: 3000, 2940, 1750, 1390 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.44 (dd, ^3J = 6.0, 0.5, H-C(5)); 4.27 (s, H-C(7)); 2.28 (dd, ^2J = 18.2, ^3J = 6.0, H_{exo}-C(4)); 2.58 (dd, ^2J =18.2, ^3J = 0.5, H_{endo}-C(4)); 1.64, 1.53, 1.47, 1.43 (4s, 4Me).
17. a) Data of (-)-**9**: m.p. 82-83°C; $[\alpha]^{25}_{589}$ = -65 (c = 1.0, $CHCl_3$); IR (KBr) ν: 2980, 2940, 2880, 1740, 1460 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.22 (s, H-C(7)); 4.10 (d, ^3J = 0.8, H-C(5)); 2.63 (dq, ^3J = 7.6, 0.8, H_{endo}-C(4)); 1.63, 1.51, 1.45, 1.42 (4s, 4Me); 1.44 (d, ^3J = 7.6, Me-C(4)); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 170.2, 113.9, 111.9 (3s), 89.8 (d), 89.3 (s), 87.0, 38.5 (2d), 28.2, 27.5, 21.5, 18.7, 17.7 (5q); b) data of (-)-**10**: m.p. 71°C, $[\alpha]^{25}_{589}$ = -56 (c = 1.0, $CHCl_3$); IR (KBr) ν: 2990, 2940, 2880, 1745, 1450 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.29 (d, ^3J = 4.8, H-C(5)); 4.25 (s, H-C(7)); 3.04 (dq, ^3J = 7.6, 4.9, H_{exo}-C(4)); 1.60, 1.52, 1.44, 1.41 (4s, 4Me); 1.31 (d, ^3J = 7.6, Me-C(4)); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ_C: 170.7, 113.9, 112.3 (3s), 91.0 (d), 90.1 (s), 85.9, 41.1 (2d), 28.5, 27.6, 22.7, 18.4, 11.4 (5q).
18. Data of (-)-**12**: m.p. 41°C, $[\alpha]^{25}_{589}$ = -67 (c = 1.0, $CHCl_3$); IR (KBr) ν: 3450, 2960, 2930, 2890, 2860, 1775, 1715, 1470 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ_H: 4.25 (d, ^3J = 7.4, H-C(3)); 4.05 (d, ^3J = 5.2, H-C(5)); 3.73 (d, ^3J = 5.2, HO-C(5)); 2.59 (dq, ^3J = 7.4, 7.5, H-C(2)); 2.40 (s, H_3-C(7)); 1.38 (d, ^3J = 7.5, Me-C(2)); 1.14 (s, Me-C(4)); 0.89 (s, *t*-Bu); 0.13, 0.12 (2s, Me_2Si).
19. a) Data of (+)-**17**: viscous oil, $[\alpha]^{25}_{589}$ = +8.6 (c = 0.5, MeOH); IR (CH_2Cl_2) ν: 3750, 3450, 2920, 2890, 2640, 1770, 1380 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 4.31 (d, ^3J = 9.3, H-C(3)); 3.89 (dq, ^3J = 6.2, 6.3, H-C(6)); 3.53 (d, ^3J = 6.2, H-C(5)); 2.68 (dq, ^3J = 9.3, 7.1, H-C(2)); 1.44 (s, Me-C(4)); 1.31 (d, ^3J = 6.3, H_3-C(7)); 1.29 (d, ^3J = 7.1, Me-C(2)); ^{13}C-NMR (100.6 MHz, CD_3OD) δ_C: 178.8, 89.9 (2s), 79.4, 75.7, 68.7, 43.4 (4d), 20.2, 18.0, 12.9 (3q); b) data of (+)-**18**: m.p. 129-130°C, $[\alpha]^{25}_{589}$ = +14 (c = 1.0, MeOH); IR (KBr) ν: 3500, 3430, 2990, 2940, 2900, 2880, 1720, 1450, 1380 cm^{-1}; ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 4.39 (d, ^3J = 10.4, H-C(3)); 4.02 (dq, ^3J = 1.8, 6.4, H-C(6)); 3.53 (d, ^3J = 1.8, H-C(5)); 2.76 (dq ^3J = 10.4, 7.0, H-C(2)); 1.39 (s, Me-C(4)); 1.33 (d, ^3J = 6.4, H_3-C(7)); 1.30 (d, ^3J = 7.0, Me-C(2)); ^{13}C-NMR (100.6 MHz, CD_3OD) δ_C: 178.6, 90.0 (2s), 77.6, 74.1, 67.8, 42.1 (4d), 20.6, 17.4, 13.0 (3q).
20. All the new compounds described here gave satisfactory elemental analyses. Details will be given in a forthcoming full paper.

(Received in France 8 February 1993; accepted 12 February 1993)