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Polypropionate Fragments with Four Contiguous Chiral Centres from Acetone

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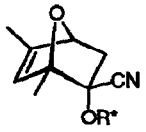
Abstract: *The Diels-Alder adduct of 2,4-dimethylfuran and 1-cyanovinyl acetate was converted with high stereoselectivity into 1,3,5-trimethylcyclohexen-4,6-diol derivatives that can be cleaved into protected polypropionate fragments.*

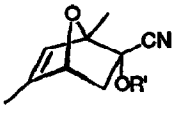
Keywords: *1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl, S_N2' ring opening, (3RS,4SR,5SR,6SR)-4,6-dibenzyloxy-1,3,5-trimethylcyclohexene, (2RS,3SR,4RS,5RS)-3,5-dibenzyloxy-2,4-dimethyl-6-oxoheptanal.*

A large variety of natural products of biological interest contain polypropionate fragments (chains with alternating hydroxyl and methyl substituents).[1] Several synthetic methods have been proposed to obtain these systems.[2,3] Recently, we have shown[2] that 2,4-dimethylfuran (obtained in 3 steps from acetone[4]) can be readily converted into optically pure 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives such as (-)-**1** and (+)-**2**. After double hydroxylation of the olefinic moiety of (-)-**1** and several transformations the doubly branched heptono-1,4-lactones (+)-**3** and (+)-**4** were obtained with high stereoselectivity.[2]



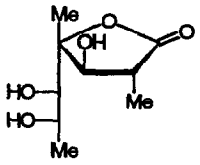
(-)-**1**

R*=(1*S*)-camphanoyl

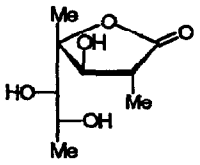


(+)-**2**

R'=(1*R*)-camphanoyl



(+)-**3**

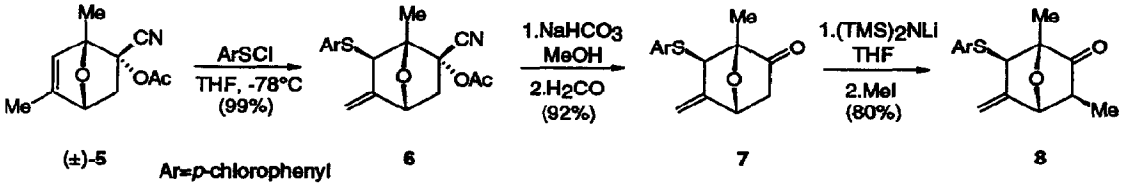


(+)-**4**

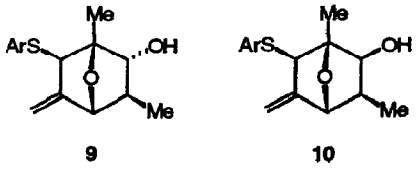
We report here a new approach to the synthesis of polypropionate fragments starting with the Diels-Alder adduct **5** of 2,4-dimethylfuran to 1-cyanovinyl acetate.[5] It relies on the ethereal ring opening of 7-oxabicyclo[2.2.1]heptenes following a method developed by Plumet and co-workers.[6]

Reaction of **5** (THF, -78°C → 20°C) with *p*-chlorobenzenesulfenyl chloride (one equivalent), followed by work-up with aqueous $NaHCO_3$ gave **6** in nearly quantitative yield.[7] Saponification of the cyanoacetate moiety of **6** under usual conditions (MeONa/MeOH then H_2CO)[8] led to isomerization of the alkene with formation of 6-(*p*-chlorophenylthio)-1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one. Under milder conditions ($NaHCO_3$/MeOH, then H_2CO) the desired methylene ketone **7** could be obtained in 92% yield. The *exo* configuration of the arylthio substituent in **6** was expected for steric reasons[8,9] and was confirmed in compound **10** described below. The lithium enolate of **7**, obtained by deprotonation with $(Me_3Si)_2NLi$ (THF, -78°C), was quenched with MeI (-78°C) and afforded the product of mono α-methylation **8** (80%).[10] The high *exo* facial selectivity of this alkylation was expected for steric reasons.[9,11] It was confirmed by the absence of vicinal coupling between protons H-C(4) and H_{endo}-C(3).[12,13] Depending on the nature of the reducing agent,

ketone **8** could be transformed either into *endo* alcohol **9** or its *exo* isomer **10** (see Table).[14] With L-Selectride ($LiB[CH(Me)Et]_3H$) only the *exo* alcohol **10** was formed and it was isolated in 87% yield. In this case, the *exo* methyl group at C(3) impedes the approach of the reagent to the carbonyl moiety onto its *exo* face.[15] The NOESY experiment with **10** showed interactions between protons H-C(2), H-C(3) and H-C(6) and thus proved the *exo* configuration of the C(2), C(3) and C(6) substituents in this compound. With reagents such as DIBAH (diisobutylaluminium hydride) or mixed hydrides resulting from the combination of $NaBH_4$ with Lewis acids, concurrent attack on the *exo* face of the bicyclic ketone **8** becomes possible, perhaps because of coordination with the 7-oxa bridge. The best yield (73%) of *endo* alcohol **9** was obtained with a 4:1 mixture of $ZnCl_2 \cdot Et_2O$ and $NaBH_4$ in dry ether at 0°C.



(±)-5 Ar=*p*-chlorophenyl **6** **7** **8**

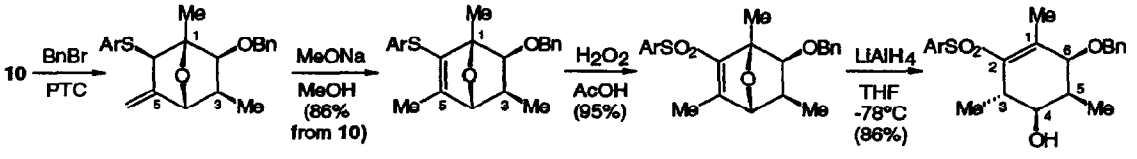


9 **10**

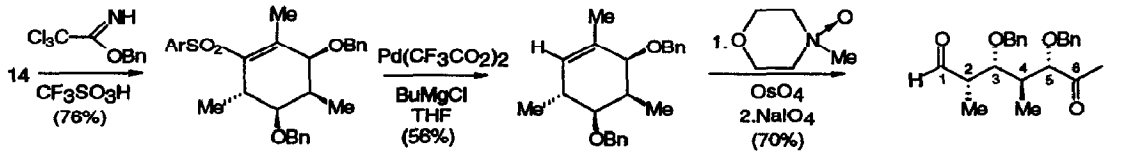
Table. Reduction of **8** → **9** + **10**

Conditions	9:10	Yield
L-Selectride/THF, -78°C	<5:95	87%
Li(*t*-BuO)$_3$AlH/THF, 20°C	1:5.5	95%
$NaBH_4$/EtOH/H_2O, 20°C	1:2.2	97%
DIBAH/CH_2Cl_2, -78°C	1:1.4	95%
$NaBH_4$+ZnI_2/Et_2O, 0°C	3:1	>90%
$NaBH_4$+$ZnCl_2$/Et_2O, 0°C	7.3:1	83%

Benzylation of **10** under phase transfer catalysis conditions (BnBr, toluene, 50% NaOH/H_2O, Bu_4NBr)[16] furnished **11** which was isomerized into the 7-oxanorbornene derivative **12** (86% based on **10**) on treatment with MeONa in MeOH (reflux). The reaction was accompanied by the formation of 5% of benzyl 6-*endo*-(*p*-chlorophenylthio)-1,3-*exo*-dimethyl-5-methylene-7-oxabicyclo[2.2.1]hept-2-*exo*-yl ether (C(6)-epimer of **11**).



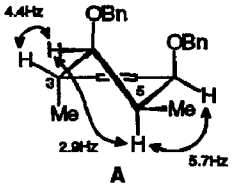
11 **12** **13** **14**



15 **16** **17**

Oxidation of **12** with H_2O_2 in AcOH (20°C) afforded the corresponding sulfone **13** (95%).[17] Treatment of **13** with $LiAlH_4$ in THF at -78°C[6a,18] yielded the cyclohexenediol derivative **14** (86%) with high stereoselectivity. Hydride addition to the sulfonyl substituted double bond in **13** was expected to prefer the *exo* face of

the bicyclic system for steric reasons and because of the possible pre-coordination of $LiAlH_4$ to the 7-oxa bridge. The structure of **14** was confirmed by its spectral data and that of the corresponding dibenzyl diether **15**[19] obtained in 76% yield by treatment with benzyl 2,2,2-trichloroacetimidate in the presence of a catalytic amount of CF_3SO_3H.[20,21] The cyclohexane derivatives **14** and **15** probably adopt the pseudo chair conformation **A** suggested by the NOESY spectrum of **15** that showed significant NOE's between the proton signals of Me-C(3) and H-C(5).



A

Attempts to cleave the double bond of **15** with ozone, $KMnO_4$/18--crown-6, OsO_4/PDC, $NaIO_4/RuCl_3$[22] or H_2CrO_4 were not successful. Desulfonation with Al/Hg[23] or sodium dithionite[24] also failed. Finally we found that the treatment of **15** with butylmagnesium chloride in THF in the presence of $Pd(acac)_2$ or $Pd(CF_3COO)_2$[25] afforded **16** (56%). Direct cleavage of the C=C double bond of **16** with O_3, $RuCl_3/NaIO_4$[22] or $OsO_4/NaIO_4$ gave intractable mixtures of products. Dihydroxylation of **16** with *N*-methylmorpholine *N*-oxide and a catalytic amount of OsO_4 (THF/*t*-BuOH/H_2O 12:10:1, 20°C, 54 h) gave a 4:3 mixture of diastereomeric diols which was oxidized with $NaIO_4/NH_4Cl$/MeOH into the 6-oxoheptanal **17** (70% based on **16**).[26,27]

This report demonstrates the possibility of conversion of acetone into polypropionate fragments containing four contiguous chiral carbon centres in a highly stereoselective fashion and as homochiral synthons since the optically pure intermediates (-)-**1** and (+)-**2** are readily available.[28] Work is underway to define conditions that will transform (-)-**1** and (+)-**2** into all possible stereomers of **17** and analogues.

Acknowledgements. We are grateful to the *Swiss National Science Foundation* (program CHiral 2), *Hoffmann-La Roche AG* (Basel), and the *Fonds Herbette* (Lausanne) for financial support. We also thank the European COST Chemistry D2 program for supporting the cooperation between the research group of Prof. Plumet (Madrid) and our group.

References and Notes

1. See e.g.: Rinehart, K. L. Jr.; Shield, L. S. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 231-307; 23; Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2-72; Paterson, I.; Mansuri, M. M. *Ibid.* **1985**, *41*, 3569-3624; Boivin, T. L. B. *Ibid.* **1987**, *43*, 3309-3362; Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101-103 and ref. cited therein.
2. Kernen, P.; Vogel, P. *Tetrahedron Lett.* **1993**, *34*, 2473-2476 and ref. 2-4 of this paper.
3. For recent syntheses, see e.g.: Eshelman, J. E.; Epps, J. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 749-752; Evans, D. A.; Ng, H. P. *Ibid.* **1993**, *34*, 2229-2232; Zhao Y.-b.; Pratt, N. E.; Heeg, M. J.; Albizati, K. F. *J. Org. Chem.* **1993**, *58*, 1300-1301; Tirado, R.; Prieto, J. A. *Ibid.* **1993**, *58*, 5666-5673; Paterson, I.; Tillyer, R. D. *Ibid.* **1993**, *58*, 4182-4184; Carretero, J. C.; Dominguez, E. *Ibid.* **1993**, *58*, 1596-1600; White, J. D.; Porter, W. J.; Tiller, *Synlett* **1993**, 535-538; Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621-12622; Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *Ibid.* **1993**, *115*, 4419-4420; Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *Ibid.* **1993**, *115*, 7906-7907; Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *Ibid.* **1993**, *115*, 9345-9346.
4. Morel, T.; Verkade, P. E. *Rec. Trav. Chim. Pays-Bas* **1949**, *68*, 619-638; **1951**, *70*, 35-49.
5. Kernen, P. Ph. D. thesis, Ecole Polytechnique Fédérale de Lausanne, 1994.
6. a) Arjona, O.; Fernández de la Pradilla, R.; Mallo, A.; Plumet, J.; Viso, A. *Tetrahedron Lett.* **1990**, *31*, 1475-1478; b) see also: Arjona, O.; Martin-Domenech, A.; Plumet, J. *J. Org. Chem.* **1993**, *58*, 7929-7931; Lautens, M. *Synlett* **1993**, 177-185; Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193-1194.
7. For analogous transformations, see e.g.: Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208-1217.

8. Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341-5348.
9. Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348-5353.
10. Data of **6**: m.p. 108-109°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.37-7.30 (m, Ar), 5.26 & 5.19 (2m, CH_2=CH(5)), 4.80 (d, ^3J = 5.8 Hz, H-C(4)), 4.38 (s, H-C(6)), 3.01 (dd, ^2J= 14.3, ^3J = 5.8, H_{exo}-C(3)), 2.18 (s, AcO), 2.01 (d, ^2J = 14.3, H_{endo}-C(3)), 1.79 (s, Me-C(1)). Data of **7**: m.p. 76°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.38-7.27 (m, Ar), 5.36 & 5.27 (2m, H_2C=C(5)), 5.04 (d, ^3J = 5.6, H-C(4)), 3.84 (s, H-C(6)), 2.67 (dd, ^2J = 17.3, ^3J = 5.6, H_{exo}-C(3)), 2.20 (d, ^2J = 17.3, H_{endo}-C(3)), 1.45 (s, Me-C(1)); IR (KBr) $\nu_{C=O}$: 1750 cm^{-1}.
11. Attempts to monomethylate 1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-one[2] under similar conditions led only to aldolization of the ketone.
12. Data of **8**: m.p. 81-82°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.36 & 7.27 (2m, Ar), 5.35 & 5.27 (2m, H_2C=C(5)), 4.61 (s, H-C(4)), 3.82 (s, H-C(6)), 2.22 (q, ^3J = 7.4, H-C(3)), 1.44 (s, Me-C(1)), 1.26 (d, ^3J = 7.4, Me-C(3)); IR (KBr) $\nu_{C=O}$: 1755 cm^{-1}.
13. Gagnaire, D.; Payo-Subiza, E. *Bull. Soc. Chim. Fr.* **1963**, 2627-2631; Ramey, K. C.; Lini, D. C. *J. Magn. Reson.* **1970**, *3*, 94-102; Nelson, W. L.; Allen, D. R. *J. Heterocycl. Chem.* **1972**, *9*, 561-568.
14. Data of **9**: m.p. 102-105°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.38 & 7.25 (2m, Ar), 5.19 & 5.13 (2m, H_2C=C(5)), 4.53 (s, H-C(6)), 4.19 (s, H-C(4)), 3.60 (m, H-C(2)), 1.96 (d, ^3J = 4.4, OH), 1.76 (qd, ^3J = 7.1, 2.8, H-C(3)), 1.47 (s, Me-C(1)), 1.18 (d, ^3J = 7.1, Me-C(3)). Data of **10**: m.p. 143-144°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.36 & 7.26 (2m, Ar), 5.16 & 5.07 (2m, H_2C=C(5)), 4.24 (s, H-C(4)), 3.79 (dd, ^3J = 9.8, 7.4, H-C(2)), 3.71 (s, H-C(6)), 2.23 (dd, ^3J = 7.4, 7.3, H-C(3)), 1.55 (d, ^3J = 9.8, OH), 1.46 (s, Me-C(1)), 1.05 (d, ^3J = 7.3, Me-C(3)).
15. Le Drian, C.; Vogel, P. *Helv. Chim. Acta* **1988**, *71*, 1399-1405.
16. Szeja, W. *Polish J. Chem.* **1981**, *55*, 1503.
17. Data of **12**: oil; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.34-7.18 (m, Ar, Ph), 4.53 (s, CH_2Ph), 4.31 (s, H-C(4)), 3.40 (d, ^3J = 6.8, H-C(2)), 2.00 (m, H-C(3)), 1.90 (s, Me-C(5)), 1.34 (s, Me-C(1)), 1.12 (d, ^3J = 7.2, Me-C(3)). Data of **13**: m.p. 108-110°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.79 & 7.50 (2m, Ar), 7.33 (m, Ph), 4.56 (m, CH_2Ph), 4.24 (s, H-C(4)), 3.67 (d, ^3J = 6.9, H-C(2)), 2.29 (s, Me-C(5)), 2.07 (m, H-C(3)), 1.47 (s, Me-C(1)), 1.10 (d, ^3J = 7.2, Me-C(3)); IR (KBr) ν_{SO_2}:1305, 1140 cm^{-1}.
18. The vinyl sulfide **12** was unreactive toward $LiAlH_4$/THF.
19. Data of **14**: m.p. 125-127°C; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.82 & 7.49 (2m, Ar), 7.33-7.31 & 7.17-7.13 (2m, Ph), 4.68 (m, CH_2Ph), 3.78 (d, ^3J = 4.1, H-C(6)), 3.65 (brd, ^3J = 8.8, H-C(4)), 3.43 (d, ^3J = 8.8, OH), 3.18 (m, H-C(3)), 2.15 (m, H-C(5)), 1.97 (d, ^5J = 1.2, Me-C(1)), 1.33 (d, ^3J = 7.1, Me-C(5)), 1.26 (d, ^3J = 7.0, Me-C(3)). Data of **15**: oil; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.73 & 7.33-7.23 (2m, Ar, 2 Ph), 4.56-4.53 (m, 2 CH_2Ph), 3.92 (d, ^3J = 5.7, H-C(6)), 3.37 (dd, ^3J = 4.4, 2.9, H-C(4)), 3.13 (m, H-C(3)), 2.38 (m, H-C(5)), 1.97 (s, Me-C(1)), 1.34 (d, ^3J = 6.8, Me-C(3)), 1.11 (d, ^3J = 7.0, Me-C(5)).
20. Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. I*, **1985**, 2247-2250.
21. Benzylation under alkaline conditions[16] led to the formation of benzene derivatives.
22. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
23. Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1973**, 351-352.
24. Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, *23*, 3265-3266.
25. Fabre, J.-L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311-4314.
26. Data of **16**: oil; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 7.45-7.36 (m, 2 Ph), 5.22 (m, H-C(2)), 4.64 & 4.61 (2m, 2 CH_2Ph), 4.05 (m, H-C(6)), 3.20 (dd, ^3J = 9.4, 3.5, H-C(4)), 2.78 (m, H-C(3)), 2.39 (m, H-C(5)), 1.81 (s, Me-C(1)), 1.12 (d, ^3J = 6.9, Me-C(5)), 1.04 (d, ^3J = 6.9, Me-C(3)). Data of **18**: oil, cannot be kept in the condensed state; ^{1}H-NMR ($CDCl_3$, 250 MHz) δ_H: 9.77 (d, ^3J = 0.4, CHO), 7.39-7.21 (m, 2 Ph), 4.60 & 4.34 (2m, 2 CH_2Ph), 4.16 (dd, ^3J = 9.0, 2.2, H-C(3)), 3.79 (d, ^3J = 3.6, H-C(5)), 2.50 (m, H-C(2), H-C(4)), 2.06 (s, MeCO), 1.16 (d, ^3J = 7.0, Me-C(4)), 1.00 (d, ^3J = 7.1, Me-C(2)); ^{13}C-NMR ($CDCl_3$, 100.69 MHz) δ_C: 209.0 (s, C(6)), 204.0 (d, ^1J = 167, CHO), 137.7 & 137.6 (2s, 2 Ph), 128.4, 128.2, 128.0, 127.9, 127.7 & 127.5 (6d, ^1J = ~160, 2 Ph), 86.2 (d, ^1J = 140, C(3) or C(5)), 77.5 (d, ^1J = 136, C(3) or C(5)), 73.2 & 72.5 (2t, ^1J = 143, 2 CH_2Ph), 48.9 (dd, ^1J = 122, ^2J = 23, C(2)), 39.5 (d, ^1J = 129, C(4)), 26.6, 14.4 & 6.9 (3q, ^1J = 128, 3 Me).
27. All new compounds were fully characterized by their spectral data and elemental analyses.
28. Homochiral **17** is a potential intermediate in the synthesis of aplysiatoxin, see e.g.: Okamura, H.; Kuroda, S.; Ikegami, S.; Tomita, K.; Sugimoto, Y.-i.; Sakaguchi, S.-i.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1993**, *49*, 10531-10554.

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