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'Naked sugars of the second generation': Asymmetric synthesis of long-chain polypropionates and analogues starting with acetone

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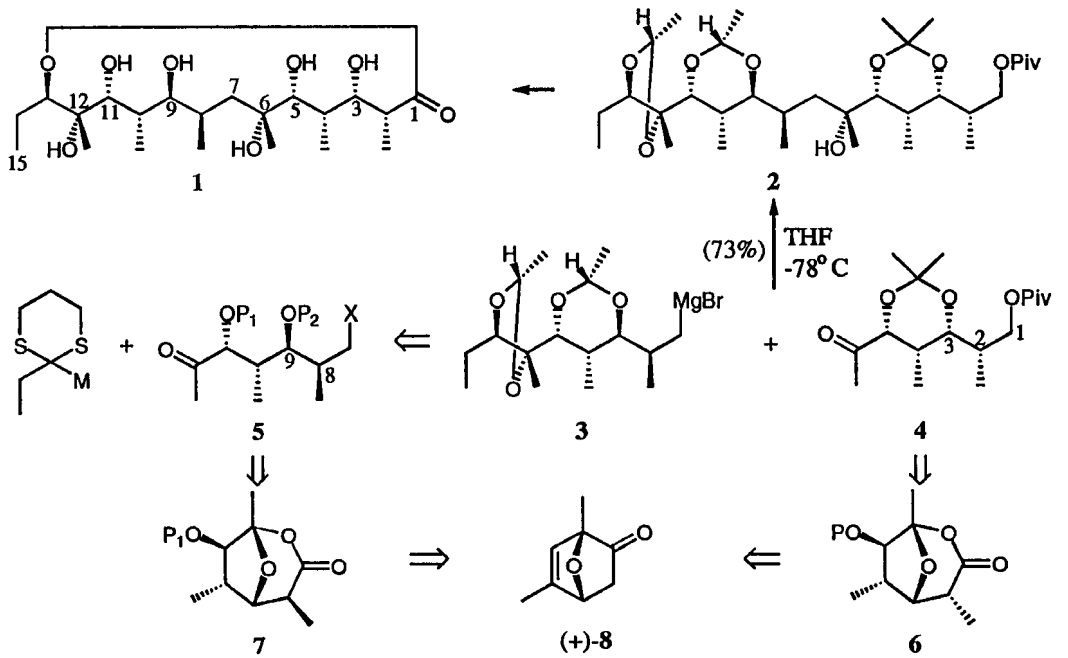
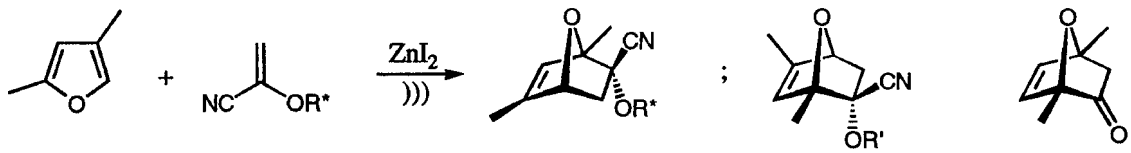
Abstract: Homochiral Diels-Alder adduct of 2,4-dimethylfuran to 1-cyanovinyl (1'R)- or (1'S)-camphanate are transformed readily into polypropionate fragments containing four or five contiguous stereogenic centres. They can be condensed *via* cross-aldolizations to lithium enolates of 7-oxabicyclo[2.2.1]heptan-2-ones with high diastereoselectivity generating long--chain systems containing up to eleven stereogenic centres and tertiary alcoholic moieties.

A large variety of natural products of biological interest contain polypropionate fragments (chain with alternating hydroxy and methyl substituents).[1] Among the many macrolide antibiotics, erythronolides (aglycons of erythromycins) have become the yardstick for measuring progress in the efficiency of stereoselective syntheses.[3,4] The shortest synthesis of (9S)-dihydroerythronolide A (**1**) is the linear approach of Stürmer *et al.*[3a] Other more convergent approaches[3b] imply a retrosynthetic disconnection at the C(6)--C(7) bond as illustrated with the synthesis of Stork *et al.*[4] which couples the fragments **3** and **4** to generate **2** with high diastereoselectivity. If intermediate **3** could be derived from **5** which is the 2,3-diepimer of **4**, one can envision these two polypropionate fragments and analogues to derive from the uronolactones **7** and **6**, respectively, that will be generated from the same homochiral (1R,4R)-1,5-dimethyl-7-oxabicyclo[2.2.1]-hept-5-en-2-one ((+)-**8**). This chiron and its enantiomer (-)-**8** are obtained readily.[2]

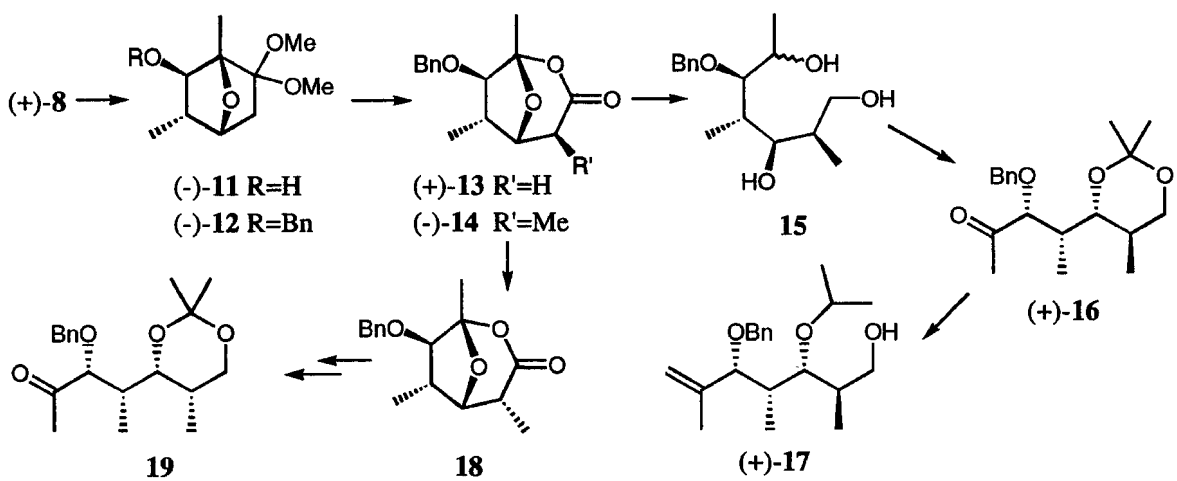


The Diels-Alder additions of 2,4-dimethylfuran to 1-cyanovinyl (1R)-camphanate and 1-cyanovinyl (1S)-camphanate (ZnI_2, sonication) give the diastereomerically pure adducts (+)-**9** and (-)-**10**, respectively, that are saponified into the corresponding enones (+)-**8** and (-)-**8** with recovery of the chiral auxiliaries (1R)- and (1S)-camphanic acid, both commercially available. The 2,4-dimethylfuran is obtained in 3 steps from acetone.[6] By analogy with other homochiral 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives,[7] we call chirons (+)-**8**, (-)-**8**, (+)-**9** and (-)-**10** "naked sugars of the second generation". We present here selected examples of their transformations into polypropionate fragments including analogues of intermediates **4** and **5**.



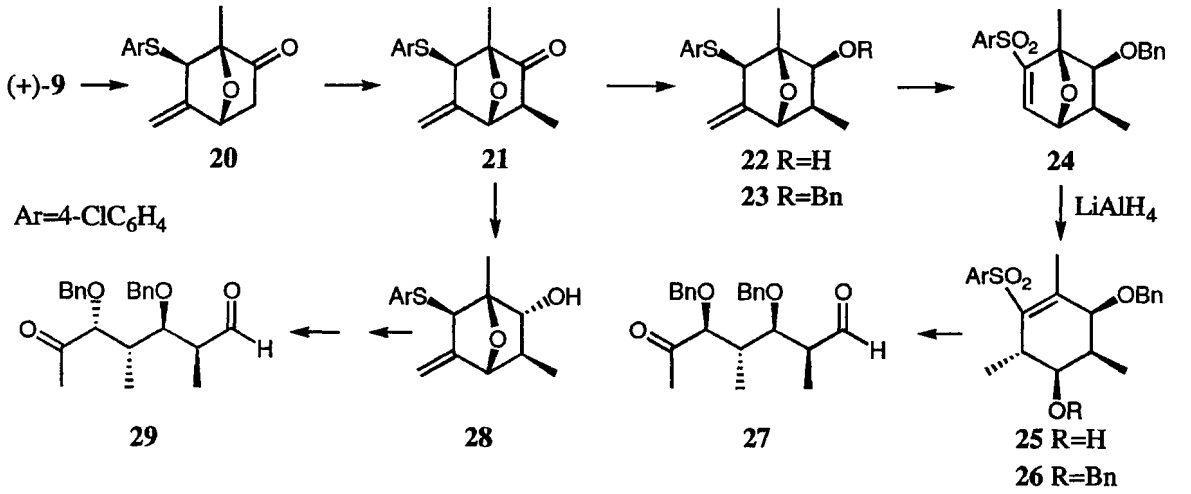
(+)-**9** (-)-**10** (-)-**8**

Hydroboration ($BH_3 \cdot Me_2S$) of the dimethyl acetal of (+)-**8** followed by oxidative work-up ($NaBO_3$) gave alcohol (-)-**11** which was then protected as its benzyl ether (-)-**12**. Acetal hydrolysis followed by regiospecific Baeyer-Villiger oxidation (*m*CPBA/$NaHCO_3$) provided uronolactone (+)-**13**, the conjugate base of which generated with $(Me_3Si)_2NLi$ reacted stereoselectively onto its *exo* face with MeI to give (-)-**14**. Reduction of (-)-**14** with $LiAlH_4$ led to triols **15**, the partial protection of which with dimethoxypropane ($SnCl_2$) and oxidation afforded methyl ketone (+)-**16**, 9-epimeric analogue of intermediates of type **5**. Reaction of (+)-**16** with $MePPh_3Br/NaNH_2$ followed by DIBAH reduction of the acetonide gave (+)-**17**, another polypropionate fragment with four contiguous stereogenic centres in which two of the alcoholic moieties bear orthogonal protective groups. An analogue of the polypropionate fragment **4** can be reached in a similar way from uronolactone (-)-**14**. Deprotonation with $(Me_3Si)_2NLi$ (-50 °C) followed by protonation with MeOH (-60 °C) gave **18** which can be transformed, as above, into **19**.

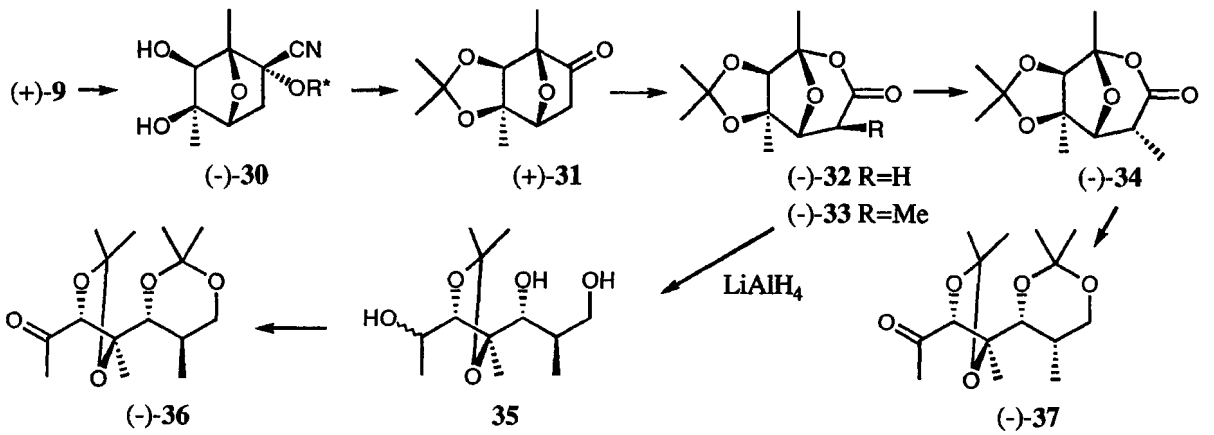


Other polypropionate fragments with four contiguous stereogenic centres can be obtained from (+)-**9** and (-)-**10** in the following fashion which implies S_N2' ring opening of the 7-oxa bridge[8] of 1,3,5-trimethyl--7-oxabicyclo[2.2.1]hept-5-en-2-ols into 1,3,5-trimethylcyclohexene-4,6-diol derivatives.[9] Reaction of (+)-**9** with *p*-chlorobenzenesulfenyl chloride, followed by work-up with $NaHCO_3$/MeOH, then aq. H_2CO, furnished **20** (92%). Its lithium enolate ($(Me_3Si)_2NLi$/THF, -78 °C) was quenched with MeI and afforded **21** (80%). Reduction of **21** with L-selectride gave selectively the *exo* alcohol **22** (87%) which was protected as its benzyl ether **23**. Treatment of the latter with NaOMe and oxidation with H_2O_2 gave the corresponding alkenesulfone **24**, the reduction of which with $LiAlH_4$ afforded **25**. After benzylation of the cyclohexenol, reductive cleavage of the phenylsulfone moiety (BuMgCl, $Pd(acac)_2$) and oxidative cleavage

of the C=C double bond with $NaIO_4/NH_4Cl$/MeOH led to the 6-oxoheptanal **27**. Reduction of **21** with $ZnCl_2{\cdot}Et_2O$ and $NaBH_4$ (Et_2O) furnished the *endo* alcohol **28** which can be transformed, as above, into the 6-oxoheptanal **29**.

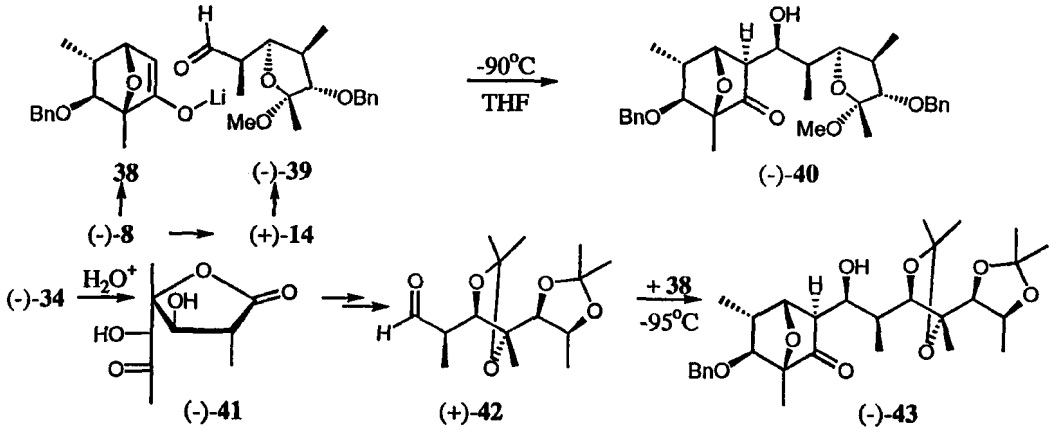


As illustrated with erythronolide **A** (**1**) many polypropionate antibiotics contain tertiary alcoholic centres. The latter can be constructed stereoselectively into complex fragments by double hydroxylation of the olefinic moiety of (+)-**9** and (-)-**10** as shown below. Dihydroxylation of (+)-**9** (N-methylmorpholine *N*-oxide·H_2O, 0.01 equiv. of OsO_4) gave *exo,exo*-diol (-)-**30** which was then protected as its acetonide. Saponification followed by treatment with formaline provided ketone (+)-**31** and allowed one to recover the chiral auxiliary (1R)-camphanic acid. Baeyer-Villiger oxidation of (+)-**31** afforded (-)-**32** (92%). Deprotonation of (-)-**32** ($(Me_3Si)_2NLi$, THF) followed by treatment with MeI yielded the *exo*-α--methyluronolactone (-)-**33**. Treatment of (-)-**33** with $(Me_3Si)_2NLi$/THF followed by quenching with MeOH led to the major *endo* α-methyllactone (-)-**34**. Reduction of (-)-**33** with $LiAlH_4$ gave triols **35** which were converted into methyl ketone (-)-**36** by treatment with 2,2-dimethoxypropane ($SnCl_2$) and oxidation.[10] Similarly, (-)-**37** was derived from (-)-**34**.



Perhaps the most interesting feature of our approach to the synthesis of polypropionate fragments lies in the possibility to combine them into long-chain systems containing up to eleven contiguous stereogenic centres *via* cross-aldolizations of polysubstituted 7-oxabicyclo[2.2.1]heptan-2-ones with the aldehydicy polypropionate fragments obtained above and others. The next example illustrates this point. Methanolysis of uronolactone (+)-**14** derived from (-)-**8** was converted into aldehyde (-)-**39** which reacted with the lithium enolate **38** (also derived from (-)-**8**) giving a **single** aldol (-)-**40** isolated in 60% yield (like mode of addition, Cram and Felkin Anh models being obeyed[13]). Another example of highly diastereoselective

cross-aldolization is shown with the condensation of the lithium enolate **38** with aldehyde (+)-**42** derived from (-)-**34** *via* acidic treatment into (-)-**41**, followed by selective reduction and protection of the alcoholic moieties. In this case aldol (-)-**43** is the major product (>95:5). When the enantiomer of **38** was allowed to react with (+)-**42** a 3:2 mixture of two aldols was obtained.



The "naked sugars of the second generation" offer one a new approach to the convergent construction of long-chain polypropionate fragments. It exploits the high *exo* facial selectivity of the 7-oxabicyclo-[2.2.1]hept-2-yl systems[13] and the high regioselectivity of the Baeyer-Villiger oxidation of 7-oxabicyclo-[2.2.1]heptan-2-ones.[14] The method implies cross aldolizations that are highly diastereoselective for matched pairs of bicyclic lithium enolates and α-methylaldehydes that lead probably to "chelated transition states" that obey the Cram and Felkin-Anh models (steric effects). Asymmetry is induced by readily available chiral auxiliaries that are recovered at the beginning of the synthesis and which allow one to generate optically pure products in both enantiomeric forms.

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