Stereodivergent Synthesis of Enantiopure Tetrahydropyrans via the Silyloxy-Cope Rearrangement of Chiral Aldol Products

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Abstract: A stereoselective synthesis of highly substituted and enantiopure tetrahydropyrans from chiral 7-hydroxy-2-alkenoic imides and esters is described. Depending on the carboxylic acid derivative the base-induced cyclization is kinetically or thermodynamically controlled to deliver either tetrahydropyran stereoisomer selectively.

Numerous biologically active natural products contain a tetrahydropyran ring as the central structural element. Most prominent members of this class of natural products are the acid ionophores, commonly known as the polyether antibiotics, with a broad spectrum of activity as antimicrobial and cardiovascular agents.[1] Accordingly, they have been challenging targets for synthetic organic chemists.[2]

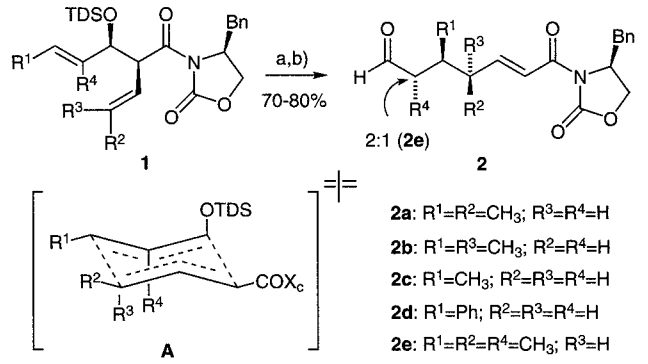
As a general synthetic strategy, the intramolecular conjugate addition of an alkoxide to an enoate has been widely used for the construction of tetrahydropyrans.[3] This cyclization is known to be a reversible process affording the tetrahydropyran as mainly one C-2 stereoisomer after the equilibrium has been reached. The preparation of the requisite chiral hydroxy enoates, however, is often quite tedious especially when additional stereogenic centers have to be incorporated into the chain.

Recently, we and subsequently others have documented extremely rapid silyloxy-Cope rearrangements of chiral *syn*-aldol products with high levels of stereocontrol.[4,5] As a first synthetic application of the multifunctional products formed upon the rearrangement we wish to report a stereoselective and very efficient synthesis of highly substituted and enantiopure tetrahydropyrans. As a special and unprecedented feature this process provides either C-2 stereoisomer selectively depending on which carboxylic acid derivative is present in the cyclization precursor.

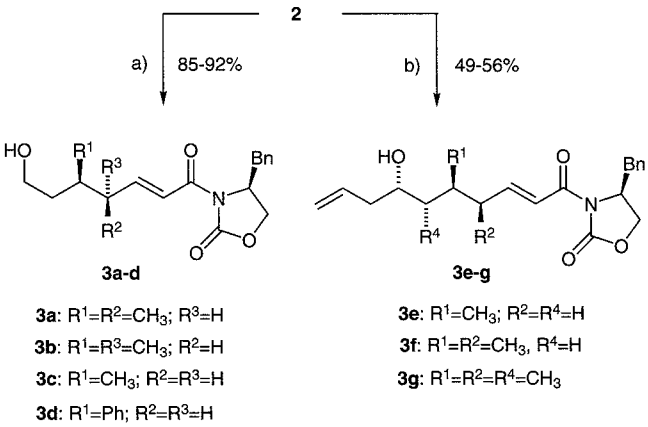
Based on well established asymmetric aldol methodology[6] the chiral, silylated *syn*-aldols **1** were prepared regio- and stereoselectively in good yields (65-72%). When the aldol products **1** were submitted to the standard conditions[4] for the Cope rearrangement (toluene, 180°C, 1-2 h) a rapid and complete rearrangement occurred. The diastereoselectivity of the silyloxy-Cope rearrangement was in the range of 15->30:1 as determined by NMR. Transition state **A** most likely accounts for the formation of **2**. The acid-catalyzed desilylation was carried out in the same flask with pTsOH. After chromatographic removal of the minor diastereomer the stereopure aldehydes **2** were obtained in 70-80% overall yield (Scheme 1). The Cope rearrangement of the tiglic aldehyde derived aldol product **1e** afforded aldehyde **2e** as a 2:1 epimeric mixture after desilylation.

The aldehydes **2a-d** were chemoselectively reduced with borane to furnish the unsaturated alcohols **3a-d** in high yield (Scheme 2). Alternatively, the aldehyde moiety in **2** was advantageously used to introduce another carbon substituent into the chain enantioselectively. By applying Brown's allylation procedure[7] allylbis(4-isocaranyl)-borane converted the aldehydes **2a**, **2c**, and **2e** to the homoallylic alcohols **3e-g** in moderate yield and high selectivity (20:1).

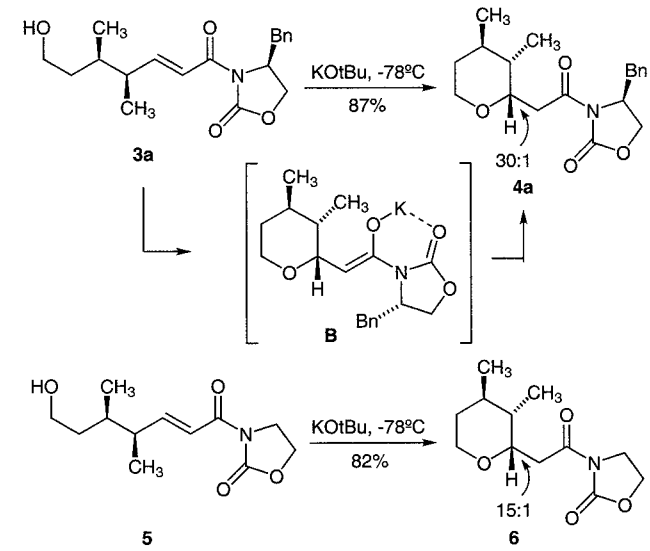
With the alcohols **3a-g** in hand the stage was set for the synthesis of the tetrahydropyrans. When **3a** was treated with KOtBu in THF at -78°C for 30 min the tetrahydropyran **4a** was formed in 87% yield with a 30:1 diastereoselection (Scheme 3).[8] Prolonged reaction times (up to 5 h) did not alter this isomeric ratio. KHMDS gave equally good results, other



Scheme 1. a) 180°C, toluene, 1-2 h; b) pTsOH, toluene, rt, 15 min; (TDS = thexyldimethylsilyl).



Scheme 2. a) BH_3, THF, 0°C, 1 h; b) $(4\text{-car})_2$BOMe, allyl magnesium bromide, Et_2O, -78°C, 1h.



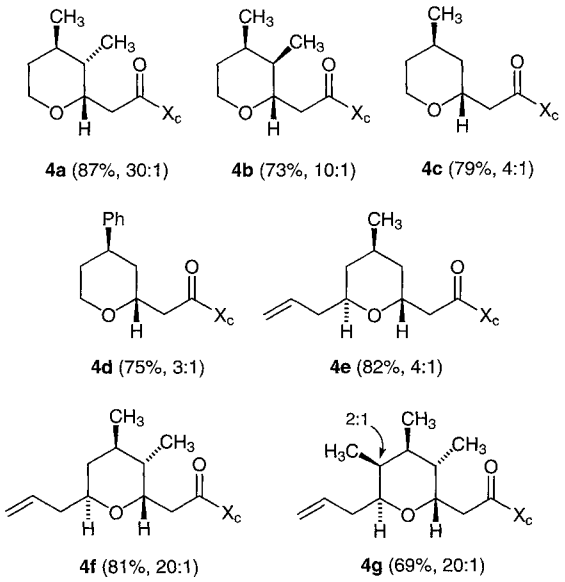
Scheme 3

bases like KH, NaH, and BuLi failed to promote the cyclization at -78°C. ^{1}H-NMR data[9] as well as a X-ray crystallographic analysis[10] unambiguously established the axial position of the acetyl imide group in **4a**. Thus, we conclude that the cyclization is kinetically controlled to afford a stable imide enolate **B** which does not undergo a retro-Michael reaction with concomitant ring opening.

In order to get some insight into the origin of stereoselectivity the cyclization was carried out with alcohol **5** bearing the achiral oxazolidinone (Scheme 3). Tetrahydropyran **6** was obtained as a 15:1 mixture of stereoisomers of which the major isomer had the same configuration at the newly formed stereogenic center at C-2 (thp numbering) as **4a**. Apparently, the stereochemical outcome of the cyclization is mainly governed by the stereogenic centers in the chain with the chiral auxiliary playing a supporting role.

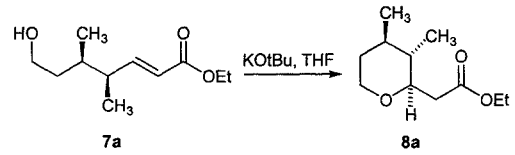
Chart 1 shows the tetrahydropyrans **4a-g** prepared in this manner with yields and selectivities of the cyclization.[8] It is worth mentioning that this process provides easy access to a wide range of polyalkyl-substituted tetrahydropyrans with high levels of stereocontrol. Even the fully substituted tetrahydropyran **4g** was prepared as a 2:1-mixture of C-5 epimers.

Chart 1. Tetrahydropyrans **4a-g** formed upon cyclization of the enimides **3a-g** (KOtBu, THF, -78°C, 30 min).[8] X_c = oxazolidinone.



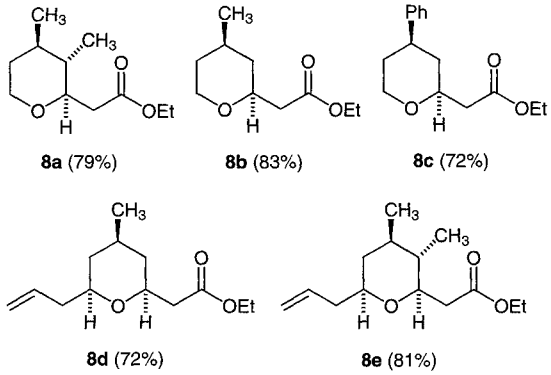
The same cyclizations were then carried out with the α,β-unsaturated esters **7** recalling the well-known thermodynamic control in the cyclization of enoates.[3] For this purpose the imides **3** were transformed into the corresponding esters **7** with $Ti(OEt)_4$/EtOH.[11] When **7a** was treated with KOtBu in THF for 30 min at -78°C a 3:1-mixture of β- and α-isomers of tetrahydropyran **8a** was formed in quantitative yield. Raising the temperature to -50°C and carrying out the cyclization for 2 h furnished the β-isomer (equatorial acetyl ester group) exclusively in 79% yield (Scheme 4). Several more 2,4-, 2,3,4- and 2,3,4,6-substituted tetrahydropyrans **8** were obtained as single stereoisomers with the opposite configuration at C-2 as compared to the tetrahydropyran acetyl imides **4** (Chart 2).

In conclusion, we have achieved a stereodivergent synthesis of highly substituted and enantiopure tetrahydropyrans. Key steps of this very efficient approach are the silyloxy-Cope rearrangement of aldol products recently developed in our laboratory and the intramolecular conjugate addition of an alkoxide to a α,β-unsaturated carboxylic acid derivative. The most attractive feature of this process is that either



Scheme 4

Chart 2. Tetrahydropyrans **8a-e** formed upon cyclization of the enoates **7a-e** (KOtBu, THF, -50°C, 2 h).



tetrahydropyran C-2 stereoisomer is available upon cyclization.[12] Extensions of this work towards the synthesis of natural products are currently underway in our laboratory.

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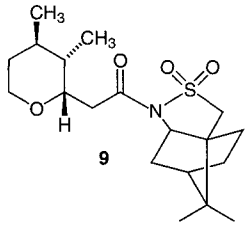
8. The stereoselectivity of the cyclization was determined by ^{1}H and ^{13}C NMR spectroscopy.

9. Spectroscopic data for **4a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ= 0.96 (d, *J*= 7.0 Hz, 3 H, CH_3), 1.03 (d, *J*= 7.0 Hz, 3 H, CH_3), 1.22 (dddd, *J*= 13.5, 8.0, 7.0, 4.0 Hz, 1 H, 5´-H_{ax}), 1.55 (dpent, *J*= 4.0, 7.0 Hz, 1 H, 3´-H_{ax}), 1.63 (dsext, *J*= 4.0, 7.0 Hz, 1 H, 4´-H_{ax}), 1.77 (ddt, *J*= 13.5, 6.5, 4.0 Hz, 1 H, 5´-H_{eq}), 2.78 (dd, *J*= 13.0, 9.5 Hz, 1 H, benzyl-H), 2.92 (dd, *J*= 15.0, 4.0 Hz, 1 H, C*H*COX_c), 3.31 (dd, *J*= 13.0, 3.0 Hz, 1 H, benzyl-H), 3.40 (dd, *J*= 15.0, 10.5 Hz, 1H, C*H*COX_c), 3.70 (ddd, *J*= 11.5, 6.5, 4.0 Hz, 1 H, 6´-H_{eq}), 3.81 (ddd, *J*= 11.5, 8.0, 4.0 Hz, 1 H, 6´-H_{ax}), 4.15 (dd, *J*= 9.0, 3.0 Hz, 1 H, 5-H), 4.19 (dd, *J*= 9.0, 7.5 Hz, 1 H, 5-H), 4.31 (dt, *J*= 10.5, 4.0 Hz, 1 H, 2´- H_{eq}), 4.69 (ddt, *J*= 9.5, 7.5, 3.0 Hz, 1 H, 4-H), 7.20-7.34 (m, 5 H, phenyl-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.5, 19.1 (2x CH_3), 31.1 (C-5´), 31.6 (C-3´/C-4´), 35.4 (CH_2COX_c), 37.7 (benzyl-C), 39.1 (C-3´/C-4´), 55.3 (C-4), 62.3 (C-5), 66.0 (C-6´), 72.7 (C-2´), 127.3, 128.9, 129.5, 135.3 (phenyl-C), 153.5 (CO), 171.6 (CO); IR (film): ν= 1782 (C=O), 1702 cm^{-1} (C=O); MS (70 eV): *m/z*= 331 (60) [M^+], 261 (40), 178 (39) [oxazolidinone], 113 (100) [M^+ - CH_2COX_c]; $[\alpha]_D^{20}$ = +20.4° (*c* = 1, $CHCl_3$); HRMS calcd for $C_{19}H_{25}NO_4$: 331.1783, found 331.1783. Spectroscopic data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.86 (d; *J*= 6.5 Hz, 3 H, CH_3), 0.96 (d, *J*= 6.5 Hz, 3 H, CH_3), 1.00-1.15 (m, 1 H, 3-H_{ax}), 1.20-1.30 (m, 1 H, 4-H_{ax}), 1.26 (t, *J*= 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.37 (dq, *J*= 4.5, 11.5 Hz, 1 H, 5-H_{ax}), 1.53 (dq, *J*= 11.5, 2.0 Hz, 1 H, 5-H_{eq}), 2.35 (dd, *J*= 15.0, 9.5 Hz, 1 H, C*H*CO_2Et), 2.65 (dd, *J*= 15.0, 3.0 Hz, 1 H, C*H*CO_2Et), 3.42 (dt, *J*= 3.0, 9.5 Hz, 1 H, 2-H_{ax}), 3.45 (dt, *J*= 2.0, 11.5 Hz, 1 H, 6-H_{ax}), 3.93 (ddd, *J*= 11.5, 4.5, 2.0 Hz, 1 H, 6-H_{eq}), 4.17 (q, *J*= 7.0 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2, 14.3, 19.9 (3x CH_3), 34.9 (C-5), 36.3 (C-3/C-4), 39.7 (CH_2CO_2Et), 42.4 (C-3/C-4), 60.4 ($CO_2CH_2CH_3$), 68.0 (C-6), 79.8 (C-2), 172.2 (CO); IR (film): ν= 1742 cm^{-1} (C=O); MS (70 eV): *m/z*= 200 (4) [M^+], 171 (10) [M^+ - Et], 143 (41), 130 (55), 113 (100) [M^+ - CH_2CO_2Et]; $[\alpha]_D^{20}$ = +1.6° (*c* = 0.5, $CHCl_3$); HRMS calcd for $C_{11}H_{20}O_3$: 200.1412, found 200.1412. All new compounds were fully characterized by NMR, IR, MS, HRMS and/or combustion analysis.

10. The oxazolidinone in **4a** was exchanged for the camphor sultam described by Oppolzer by the sequence: 1. LiOH/THF/H_2O, 2. $(COCl)_2$/DMF/CH_2Cl_2, 3. BuLi/ D-(-)-camphor sultam. The resulting tetrahydropyran **9** gave nice crystals suitable for X-ray crystallography.



9

Crystal data for (2*S*, 3*S*, 4*R*)-**9** ($C_{19}H_{31}NO_4S$): monoclinal, $P2_1$, a= 7.508(8) Å, b= 16.715(19) Å, c= 7.799(6) Å, β= 96.99(5)°, V= 971.5(16) $Å^3$, Z= 2, ρ_{calcd}= 1.263 Mg/m^3, F(000)= 400, λ= 0.71073 Å, T= 193 K, $\mu(Mo_{K\alpha})$= 0.189 mm^{-1}. Structural refinement based on 3429 independently collected reflections. *R*1= 0.0269, *wR*2= 0.0738. The structure was solved with direct methods (SHELX90, Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467). The crystal data have been deposited with the Cambridge Crystallographic Data Centre and may be ordered from: The Director, CCDC, 12 Union Road, Cambridge, CB21EZ, UK.

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