Enantioselective Synthesis of *cis*-3-Oxy-2,2,6,6-tetrasubstituted Tetrahydropyrans

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Abstract: A synthesis of *cis*-3-oxy-2,2,6,6-tetrasubstituted tetrahydropyrans has been achieved in an easy and straightforward way.

Key words: Sharpless epoxidation, nitriles, tetrahydropyrans, cyclisation, iodine

Tetrahydropyrans are present in many biologically active compounds,[1] for example in (+)-decarestrictine L,[2] an inhibitor of cholesterol biosynthesis, in antimitotic macrolides such as spongistatin,[3] and in fused tetrahydropyran ring systems from the backbone of brevetoxin B[4] and maitotoxin.[5] In these structures the tetrahydropyran units are generally *trans*-fused. The less usual *cis*-fused pyranopyrans are present in natural products such as elatenyne (**1**)[6] and halichondrin B (**2**), which has received much attention due to its extraordinary in vitro and in vivo antitumour activity (Figure 1).[7]

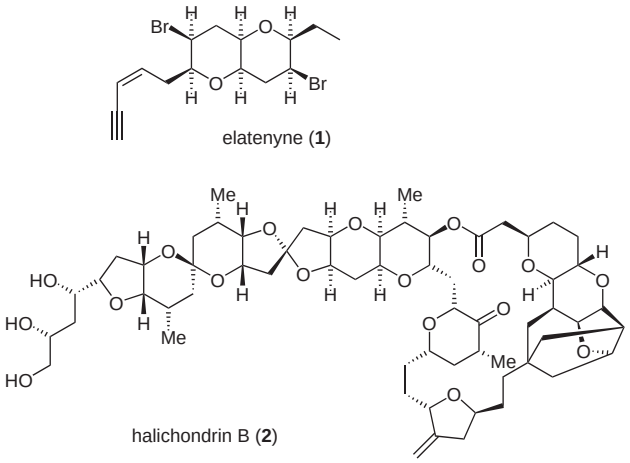
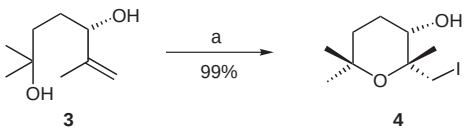


Figure 1



Scheme 1 *Reagents and conditions*: a) I_2, $NaHCO_3$, MeCN, 0 °C.

Schreiber et al.[8] described a mercury transetherification–cyclisation leading to *cis*- and *trans*-fused cyclic pyranopyrans. Suárez et al.[9] described a rearrangement of spiroacetals to give *cis*-fused 1,6-dioxadecalines and recently Martin et al.[10] described the synthesis of *cis*-2-alkyl-3-oxy-tetrahydropyran units as building blocks for new ionophores, starting from tri-*O*-acetyl-D-galactal. The most frequently used reaction for obtaining these systems is the Michael addition of an alcohol to α,β-unsaturated esters to give *cis*-2-alkyl-3-oxy-tetrahydropyrans as described by Gung et al.[11] and Martín et al.[12] Other methods for the synthesis of this kind of compound are the cyclisation of vinylstannanes with trifluoromethanesulfonic acid[13] or cyclisation of ω-oxo-γ-alkoxyallylboronates, which cyclise to *cis*-disubstituted vinyl tetrahydropyrans.[14] Very recently a version of the Michael addition has been reported using *trans*-hydroxy enones to give *cis*-2,3-disubstituted tetrahydropyrans by Taylor et al.[15]

In an earlier study we were able to synthesise *cis*-2-alkyl-3-oxy-tetrahydropyran **4** in a totally stereoselective way from olefin **3** (Scheme 1).[16] All attempts to extend the side chain were unsuccessful, so, as we were interested in enantioselectively obtaining *cis*-3-oxy-2,2,6,6-tetrasubstituted tetrahydropyrans that could be used as synthons for new ionophores, it was decided to carry out the cyclisation in a slightly more complicated substrate and study the stereoselectivity of the reaction.

The starting material for our study is the tosylate **5**, previously obtained by us,[16] whose absolute stereochemistry was established in a Sharpless epoxidation[17] step, so both enantiomers are readily available (Scheme 2). Treatment of **5** with NaCN in HMPA,[18] followed by deprotection of the tetrahydropyranyl group with *p*-TsOH in MeOH gave the α,β-unsaturated nitrile **6** in high yield. After benzylation under the usual conditions, reduction of the nitrile group to the alcohol was done with DIBAL-H[19] in two steps. The first reduction gives the aldehydes **8** and **9**, which were separated by column chromatography. The stereochemistry of the double bond in **9** was established by the NOE between the methyl and the olefinic hydrogen shown in Scheme 2. Once separated, both aldehydes were submitted separately to a further DIBAL-H reduction to give diols **10** and **11** in 80% and 78% yield, respectively.

With compounds **10** and **11** available in sufficient quantity, it was decided to study the iodine-mediated cyclisation of these compounds.

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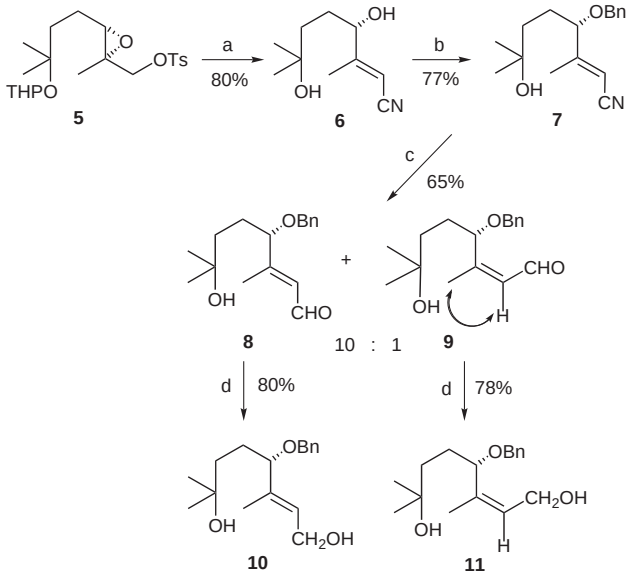
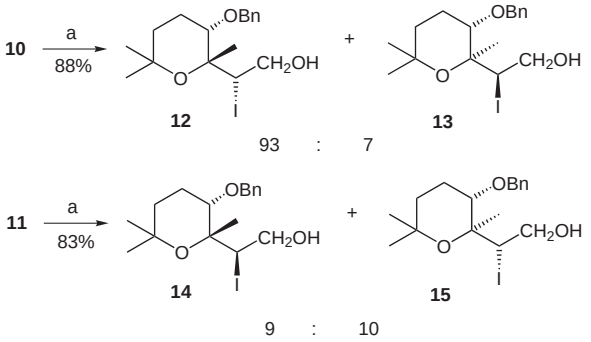


Scheme 2 *Reagents and conditions*: a) NaCN, HMPA, r.t.; *p*-TsOH, MeOH, r.t.; b) NaH, BnBr, TBAI, THF, r.t.; c) DIBAL-H, CH_2Cl_2, –78 °C; d) DIBAL-H, CH_2Cl_2, –78 °C.

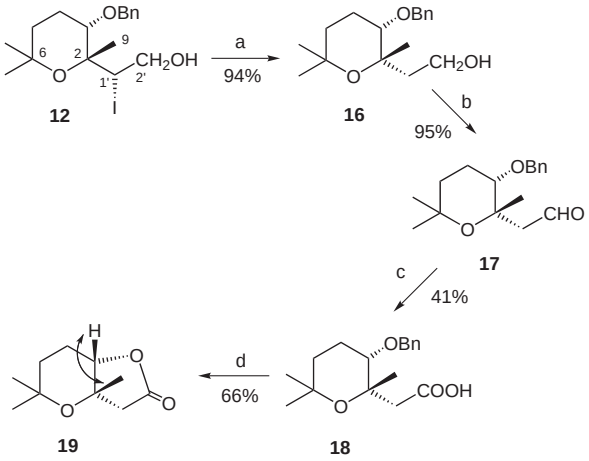
When compound **10** was submitted to treatment with iodine under kinetic conditions,[20] two tetrahydropyrans (**12** and **13**) were obtained in a ratio of 93:7 in good yield.[21] When **11** was submitted to the same conditions two different tetrahydropyrans (**14** and **15**) were obtained with practically no stereoselectivity (ratio of products 9:10, Scheme 3).



Scheme 3 *Reagents and conditions*: a) I_2, $NaHCO_3$, MeCN, 0 °C.

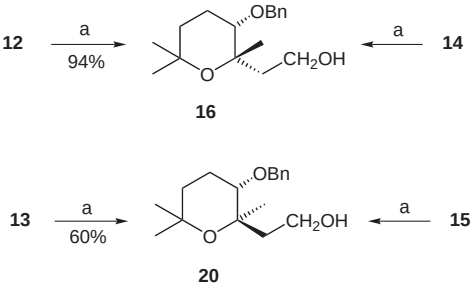
Determination of the stereochemistry of these compounds was as follows. Compound **12** was reduced with $HSnBu_3$ to give the alcohol **16**. This compound was oxidised under Swern conditions[22] to give aldehyde **17** in 95% yield. When compound **17** was left in a flask open to the air the acid **18** was obtained in moderate yield, and, if acid **18** was deprotected with H_2 on Pd/C, the reaction led to the lactone **19** (Scheme 4).[23] This compound shows a NOE between the hydrogen of C-3 and Me on C-2. In this manner the stereochemistry of C-2 was assured.

Having established the stereochemistry of compound **12** at C-2, we proceeded to do the same with the other three remaining tetrahydropyrans. Reduction with $HSnBu_3$[24] of the four tetrahydropyrans gave two diols (**16** and **20**) as



Scheme 4 *Reagents and conditions*: a) $HSnBu_3$, AIBN, C_6H_6, reflux; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C; c) O_2 (air, 24 h); d) H_2, Pd/C, EtOH, r.t.

expected. The structure of alcohol **16** has been established previously and, as the only difference between **16** and **20** is the stereochemistry of C-2, the structure for **20** is shown in Scheme 5, and so the stereochemistry for all the tetrahydropyrans at C-2 is determined. The stereochemistry of the iodide in C-1′ for all the tetrahydropyrans was established based on mechanistic grounds.



Scheme 5 *Reagents and conditions*: a) $HSnBu_3$, AIBN, C_6H_6, reflux.

The stereochemistry of these compounds can be understood by comparing the proposed transition states as shown in Figure 2.

Considering the conformational preferences of C1-oxygenated acyclic chiral alkenes for the C–C eclipsed conformation as described by Gung et al.,[25] and supposing an equatorial disposition of the benzyloxy group in the transition state, transition state **I** is more favourable than **II** for the cyclisation of the *trans* alcohol, but transition states **III** and **IV** are much the same due to the interaction of the -CH_2OH with the benzyloxy group in **III**.

Thus, a new synthesis of *cis*-3-oxy-2,2,6,6-tetrasubstituted tetrahydropyrans, synthons for the synthesis of ionophores or other uses in chemistry, has been described. The fact that the compounds can be obtained in satisfactory overall yield in both enantiomeric forms adds more versatility to the procedure.

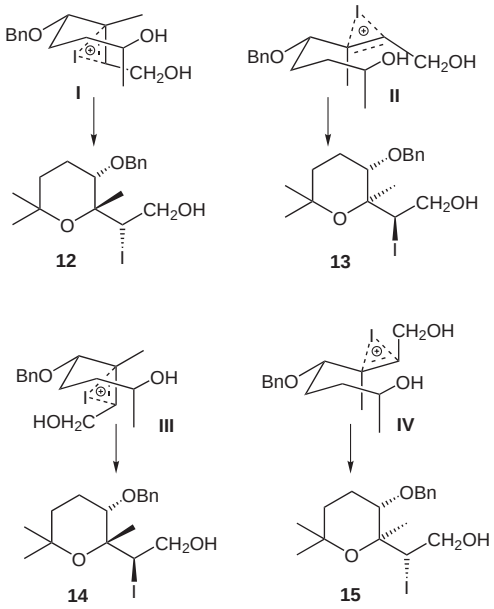


Figure 2

Acknowledgment

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(21) **Spectroscopic Data for Compound 12.** $[\alpha]_D^{20}$ +22.5 (*c* 1.0, $CHCl_3$). IR (film): 3460 (br), 2970–2870, 1454, 1377, 1221, 1069, 974, 731, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.30 (5 H, m, Ph), 4.85 (1 H, dd, *J* = 3.4, 10.1 Hz, H-1′), 4.58 (1 H, d, *J* = 10.8 Hz, OCH_2Ph, H_A), 4.48 (1 H, d, *J* = 10.8 Hz, OCH_2Ph, H_B), 4.09 (1 H, m, H_A-2′), 3.94 (1 H, m, H_B-2′), 3.43 (1 H, m, H-3), 2.05–1.85 (4 H, m, H-4, H-5), 1.51 (3 H, s, H-9), 1.26, 1.22 (3 H each, s, H-7 and H-8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.33 (C-4), 20.13 (C-9), 27.44 (C-7), 29.34 (C-5), 32.81 (C-8), 39.12 (C-1′), 66.70 (C-2′), 71.15 ($PhCH_2$), 74.04 (C-6), 75.98 (C-3), 127.47 (Ph_{para}), 127.69 (Ph_{ortho}), 128.25 (Ph_{meta}), 138.45 (Ph_{ipso}) ppm. HMRS (EI): *m/z* calcd for $C_{17}H_{26}O_3I$: 405.0927 $[M + H]^+$; found: 405.0944.

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