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Iterative asymmetric synthesis of protected *anti*-1,3-polyols

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Abstract

A new general method for the iterative asymmetric synthesis of *anti*-1,3-polyol chains has been developed. The α,α′-bisalkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone **1** with benzyloxymethylchloride as the second electrophile leads to virtually diastereo- and enantiopure substituted 2,2-dimethyl-1,3-dioxan-5-ones with good overall yields. Their deoxygenation and conversion into primary iodides affords the electrophile for the further alkylation of **1**. In this way the configurations of all new stereogenic centres are controlled by a single auxiliary.

Keywords: asymmetric synthesis; alkylation; iteration; hydrazones.

The development of highly stereoselective syntheses of 1,3-polyol chains has received considerable attention in recent years, due mainly to the growing interest in polyene-macrolides as challenging synthetic targets with desirable pharmacological features.[1] In this context, among others, the work of Rychnovsky et al. is especially noteworthy.[2] Moreover, Brückner et al. have developed several approaches to *syn*-1,3-polyols.[3] We have recently reported the synthesis of acetonide-protected *anti*-1,3-diols based on the highly diastereo- and enantioselective α,α′-bisalkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP-hydrazone **A** and subsequent deoxygenation.[4] The bisalkylation of **A** with benzyloxymethylchloride (BOMCl) as second electrophile yielded enantiopure benzyloxymethyl-substituted dioxanes **B** with good overall yields.

In this paper, we wish to present our initial results for the extension of this method towards the asymmetric synthesis of complex *anti*-1,3-polyol chains. This concept relies on the conversion of dioxanes **B** to iodides **C** by subsequent deprotection of the benzylether and functional group interchange (FGI) of the alcohol to the corresponding iodide (Scheme 1). The latter are then suitable electrophiles for the alkylation of **A** for use in an iterative process.

Accordingly, sequential alkylation of SAMP hydrazone **1** with benzylbromide and BOMCl in THF under standard conditions and cleavage of the auxiliary with aqueous oxalic acid,[5] afforded dioxanone **2** in 87% yield with diastereomeric and enantiomeric excesses of de and ee ≥96% (Scheme 2). The dioxane

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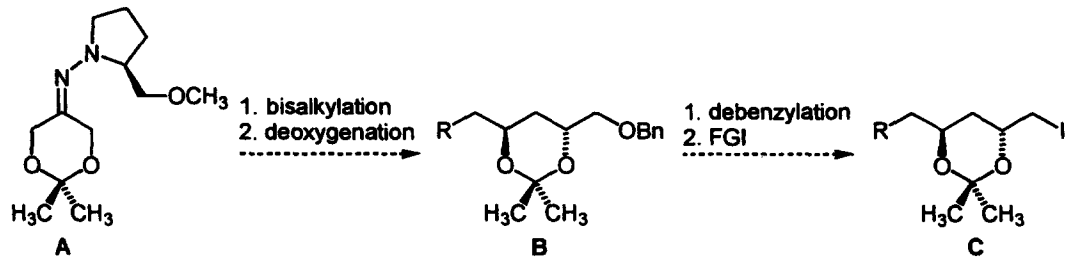
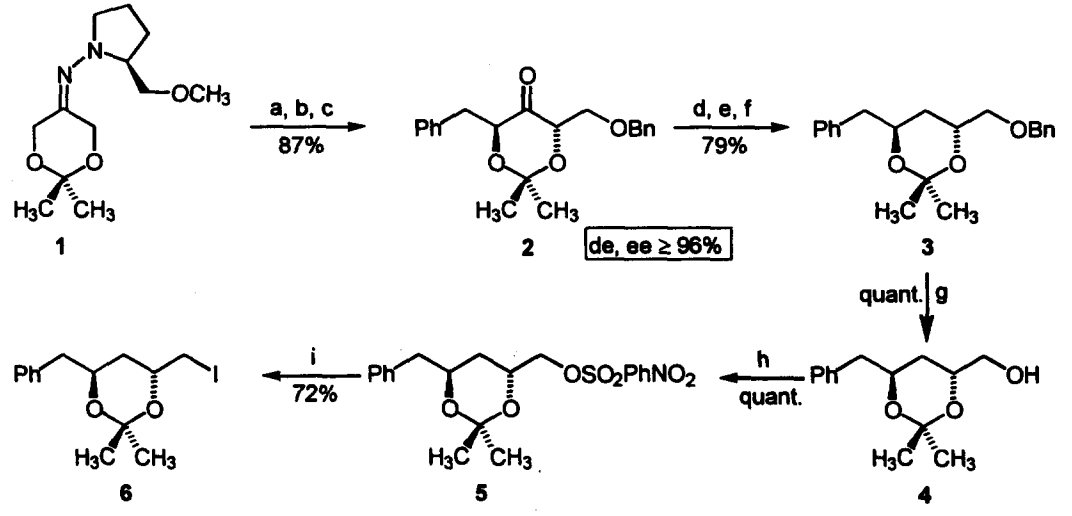


Scheme 1.

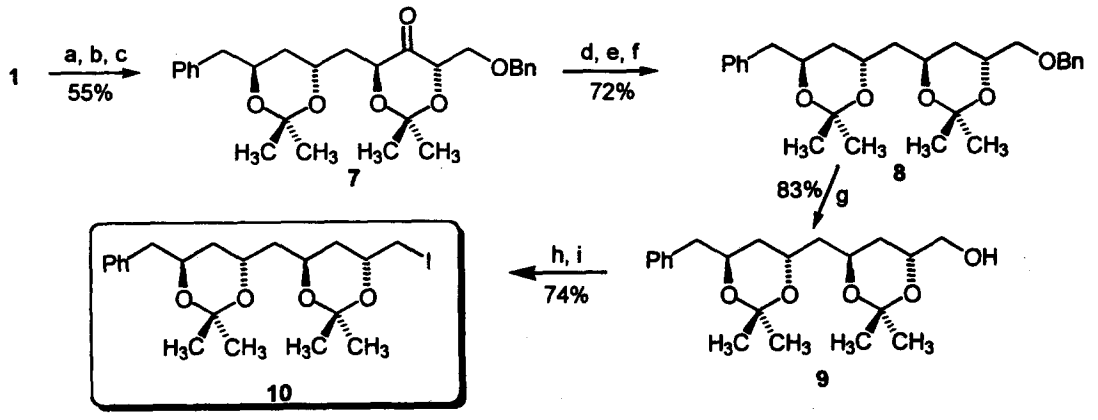
3 was isolated without any detectable epimerisation in 79% yield after deoxygenation of **2** according to the Barton–McCombie procedure,[6] and debenzylation using calcium in liquid ammonia gave alcohol **4** in quantitative yield. The use of calcium, in contrast to the more reactive lithium, circumvented a reduction of the existing phenyl ring.[7] This method was far more reliable than the palladium-catalysed hydrogenolysis, which was very sensitive to catalyst poisoning caused by traces of sulfur and tin by-products. Direct iodination of **4** by titration with iodine in the presence of triphenylphosphine and imidazole, according to Corey et al.,[8] failed due to transacetalisation of the acetonide to the more stable dioxolane. Alcohol **4** was successfully converted into the corresponding iodide **6**, according to Mori et al.,[9] via nucleophilic displacement of sulfonates. The best results were achieved using the nosylate **5**, which was obtained quantitatively from **4**. By employing the nosylate **5**, displacements with lithiumiodide occurred rapidly in DMF at 80°C in the presence of sodium bicarbonate,[10] and **6** was obtained in 72% yield after chromatographic purification.



Scheme 2. (a) 1. *t*-BuLi, THF; 2. BnBr, −105°C; (b) 1. *t*-BuLi, THF; 2. BOMCl, −105°C; (c) aq. oxalic acid, Et_2O; (d) $NaBH_4$, MeOH, −78°C (94%); (e) NaH, CS_2, MeI, THF (93%); (f) nBu_3SnH, AIBN, toluene, 100°C (91%); (g) Ca/NH_3 (l); (h) *p*-$NO_2C_6H_4SO_2Cl$, NEt_3, DMAP, CH_2Cl_2; (i) LiI, $NaHCO_3$, DMF, 80°C

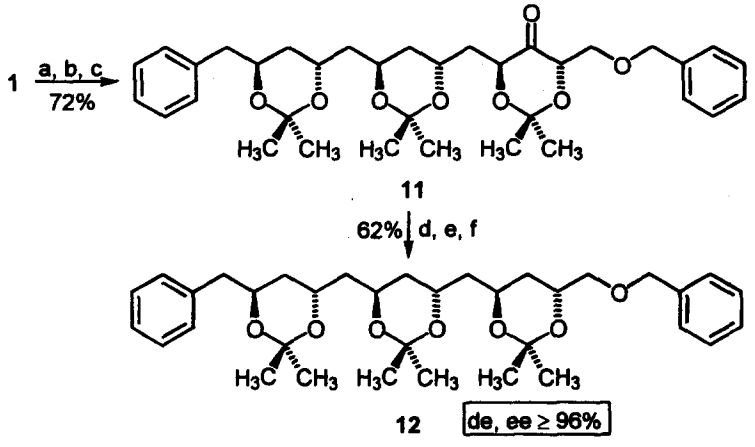
With iodide **6** in hand, the synthesis of acetonide-protected *anti*-1,3-polyols was pursued. Test reactions revealed that **6** reacted readily with the lithio aza-enolate of **1**. Gratifyingly, the sequential α,α′-bisalkylation of hydrazone **1** with iodide **6** and BOMCl was successful, and yielded dioxanone **7** in 55% yield after cleavage of the auxiliary with aqueous oxalic acid and chromatographic purification. Subsequently, the same reaction sequence (vide supra) was applied, i.e. deoxygenation of the dioxanone **7**, debenzylation of **8** and conversion of the alcohol **9** into the corresponding iodide. Thus, iodide **10** was

obtained in 44% overall yield from **7** as a new electrophile for the iterative, electrophilic alkylation of SAMP-hydrazone **1** (Scheme 3).



Scheme 3. (a) 1. *t*-BuLi, THF; 2. **6**, −105°C; (b) 1. *t*-BuLi, THF; 2. BOMCl, −105°C; (c) aq. oxalic acid, Et_2O; (d) $NaBH_4$, MeOH, −78°C; (e) NaH, CS_2, MeI, THF; (f) n-Bu_3SnH, AIBN, toluene, 100°C; (g) Ca/NH_3 (l); (h) p-$NO_2C_6H_4SO_2Cl$, NEt_3, DMAP, CH_2Cl_2; (i) LiI, $NaHCO_3$, DMF, 80°C

The reliability of this approach was finally demonstrated by sequential alkylation of hydrazone **1** with iodide **10** and BOMCl, cleavage of the hydrazone yielded dioxanone **11** in 72% yield (Scheme 4). The deoxygenation of **11** to the all-*anti*-trisdioxane **12** proceeded smoothly under standard conditions in 62% overall yield (three steps).[11]



Scheme 4. (a) 1. *t*-BuLi, THF; 2. **10**, −105°C; (b) 1. *t*-BuLi, THF; 2. BOMCl, −105°C; (c) aq. oxalic acid, Et_2O; (d) $NaBH_4$, MeOH, −78°C; (e) NaH, CS_2, MeI, THF; (f) n-Bu_3SnH, AIBN, toluene, 100°C

In summary, an efficient asymmetric synthesis of acetonide protected *anti*-1,3-polyols (de and ee ≥96%), starting from commercially available reagents, has been developed. This iterative process relies on the generation of all stereogenic centres by auxiliary controlled alkylation of 2,2-dimethyl-1,3-dioxan-5-one SAMP hydrazone and conversion of product dioxanones by functional-group interchange to primary iodides as electrophiles for the next iterative step.

Acknowledgements

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10. The addition of sodium bicarbonate is essential to prevent decomposition of the acetonide.
11. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds. Selected data for compound **12**: $[\alpha]_D^{23}$=+24.0, (*c* 1.0, acetone); IR ($CHCl_3$): $\tilde{\nu}$ (cm^{-1}) 3028 (m), 2986 (s), 2939 (s), 2859 (m), 1496 (m), 1454 (m), 1381 (vs), 1225 (vs), 1176 (s), 1128 (s), 1032 (s), 991 (m), 945 (m), 947 (m); ^{1}H NMR (300 MHz, C_6D_6): δ 1.31–1.52 (m, 28H, 6×C*H*$_3$ and 4×C*H*$_2$), 2.58 (dd, *J*=13.7 Hz, *J*=5.8 Hz, 1H, PhC*H*H), 2.88 (dd, *J*=13.7 Hz, *J*=7.4 Hz, 1H, PhCH*H*), 3.32 (dd, *J*=10.2 Hz, *J*=4.4 Hz, 1H, PhCH_2C*H*HO), 3.45 (dd, *J*=10.2 Hz, *J*=5.6 Hz, 1H, PhCH_2CH*H*O), 4.01–4.23 (m, 6H, 6×C*H*), 4.38 (d, *J*=12.1 Hz, 1H, PhC*H*HCH_2O), 4.48 (d, *J*=12.1 Hz, 1H, PhCH*H*CH_2O), 7.07–7.22 (m, 8H, H-ar), 7.30 (m, 2H, H-ar); ^{13}C NMR (75 MHz, C_6D_6): δ 24.9, 25.0, 25.1 (2×), 25.2, 25.3 (6×*C*H$_3$), 35.6, 38.9, 39.5, 42.6, 42.7 (2×), (6×*C*H$_2$), 62.95 (2×, *C*H), 63.0 (2×*C*H) 66.7 (*C*H), 67.8 (*C*H), 73.4 (2×PhCH_2CH_2O), 100.4 (*C*(CH$_3$)$_2$), 100.5 (2×, *C*(CH$_3$)$_2$), 126.4, 127.6, 127.8, 128.4, 128.5, 129.6, 139.0, 139.2 (C-ar); MS (EI, 70 eV): m/z (%) 568 (M^+–15, 3), 567 (7), 439 (3), 363 (4), 247 (4), 209 (6), 199 (9), 197 (7), 177 (9), 167 (7), 157 (11), 155 (9), 149 (11), 147 (28), 129 (17), 117 (10), 113 (8), 97 (10), 91 (100). Elemental analysis: $C_{35}H_{50}O_7$ (582.77); calcd: C, 72.13; H, 8.65; found: C, 71.99; H, 8.83.