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First enantioselective non-biological synthesis of asymmetrised tris(hydroxymethyl)methane (THYM*) and bis(hydroxymethyl)acetaldehyde (BHYMA*)†

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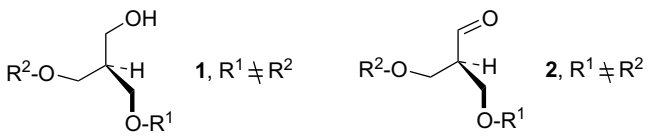
Abstract—An asymmetric synthesis of a chiral non-racemic (*O*-benzyl, *O′*-silyl) derivative of the latent C_{3v}-symmetric tris(hydroxymethyl)methane (THYM*) and of the bis(hydroxymethyl)acetaldehyde (BHYMA*) in 6 steps, 38% overall yield and 7 steps, 36% overall yield, respectively, is described starting from the commercially available 4-nitrobenzoate derivative of **17**. The method involves the Sharpless asymmetric epoxidation and a regioselective copper-mediated oxirane ring opening, as key steps.

In the context of the synthesis of new chiral non-racemic building blocks, the asymmetrised tris(hydroxymethyl)methane (THYM*, **1**) and bis(hydroxymethyl)acetaldehyde (BHYMA*, **2**) appear to be the ideal precursors to most tertiary C-branched stereogenic centres because of the versatility of their oxygenated functionalities.[1]



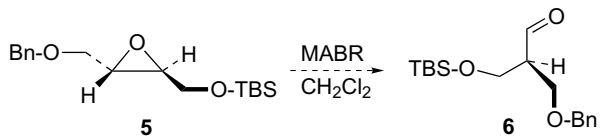
(*S*)-**3**, R^1 = Bn, R^2 = TPS; (*R*)-**3**, R^1 = TPS, R^2 = Bn

(*S*)-**4**, R^1 = Bn, R^2 = TPS; (*R*)-**4**, R^1 = TPS, R^2 = Bn

The preparation of asymmetric derivatives of **1** and **2**, mainly through enzymatic desymmetrisation of suitable diols and diacetates,[2] followed by protective and functional groups manipulation, and their use in organic synthesis has been recently summarised in a comprehensive review by Banfi and Guanti.[3] Reported yields and enantioselectivities are slightly beyond 30 and 98%, respectively.

In this paper we wish to report the first, facile, high yielding, non-enzymatic enantioselective methodology for the synthesis of both enantiomers of 2-[(benzyloxy)methyl]-3-(*tert*-butyldiphenylsilyloxy)-1-propanol (**3**)[4] and 2-[(benzyloxy)methyl]-3-(*tert*-butyldiphenylsilyloxy)-propanal (**4**), using the Sharpless asymmetric epoxidation as the key step. The benzyl and *tert*-butyldiphenylsilyl protective groups were chosen for their ideal orthogonal deprotective modes.[5]

In a first attempt, we reasoned that the simplest approach to a (*O*-benzyl, *O′*-silyl) derivative of BHYMA* **2** and, consequently, to the related THYM* **1**, would have been the stereospecific methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR)-catalysed rearrangement[6] of the readily available optically active epoxysilyl ether **5**. This Lewis acid-catalysed rearrangement of epoxides can give, in principle, the optically active (*S*)-2-[(benzyloxy)methyl]-3-(*tert*-butyldimethylsilyloxy)-propanal (**6**) in a single step.



5 **6**

Consequently, according to Scheme 1, (2*S*,3*S*)-4-(benzyloxy)-2,3-epoxybutan-1-ol (**9**)[7] was synthesised from commercially available (*Z*)-4-(benzyloxy)-2-buten-1-ol (**7**) and almost quantitatively silylated to give **5** in 73% overall yield (*e.e.* 98%).[8]

Keywords: asymmetric synthesis; epoxidation; chiral building blocks.

* Corresponding author.

† Dedicated to the memory of Professor Guido Sodano, deceased June 7th, 2001.

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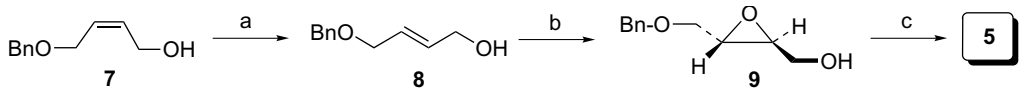


Scheme 1. (a) (i) 1.2 equiv. of pyridinium chlorochromate, Celite® (0.3 g/mmol), CH_2Cl_2, rt, 18 h; (ii) 1.4 equiv. of $NaBH_4$, MeOH −40°C, 2 h, 89%; (b) 1.0 equiv. of $Ti(O\textit{i}\text{-}Pr)_4$, 1.1 equiv. of (+)-DET, 2.0 equiv. of *t*-BuOOH, CH_2Cl_2, −18°C, 18 h, 84%, (*e.e.* 98%); (c) 1.5 equiv. of TBDMS-Cl, 2 equiv. of imidazole, DMF, 0°C, 2 h, 98%.

Unfortunately, the organoaluminum-promoted rearrangement of **5** failed to give the expected β-branched aldehyde **6**. Even forcing the reaction conditions with the use of higher reaction temperatures (though still at or below 0°C) and increasing the equivalents of MABR (from 0.2 to 1.0 or 2.0 equiv.) we recovered the unaltered starting material.[9]

In consideration of the stability of **5** to MABR, we turned our attention to the supposed more reactive substrate **11**. The parent epoxide **10** was enantiosectively prepared in 95% *e.e.*[8] following a known procedure.[10] Standard silylation and stoichiometric[11] Yamamoto's rearrangement[6] (Scheme 2) on silyl ether **11** induced an unexpected extended rearrangement affording an unstable adduct which was tentatively assigned as **12**.[12]

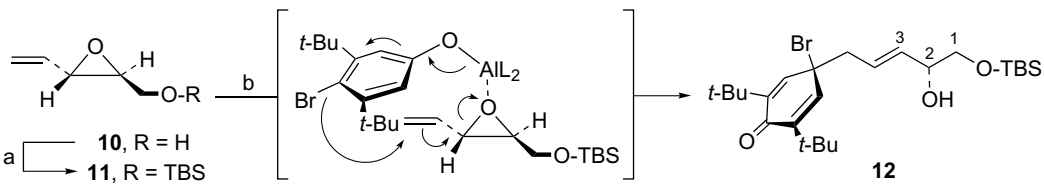
In view of these discouraging results we turned our attention back to the *trans*-epoxide **9**. This time our plan relied on a regioselective copper-mediated oxirane ring opening,[13] using a vinyl moiety as a C_1-masked unit. Thus, stereospecific opening of the oxirane **9** with vinylmagnesium bromide in the presence of cuprous iodide led to the desired monoprotected (2*R*,3*R*)-4-(benzyloxy)-2-ethenyl-butan-1,3-diol (**13**) and its regioisomer in a 83:17 ratio (Scheme 3). Control of the reaction temperature, choice of the optimal reagents' concentration (0.05 M, for **9**) and solvents ratio were crucial to the success of the ring opening, since at low temperature the reaction proceeded very slowly while higher concentration resulted in lower regioselectivity. The minor, undesired, 1,2-diol was oxidatively cleaved with sodium periodate[14] to facilitate the purification of the desired 1,3-diol **13**.

Regioselective silylation with *tert*-butyl-diphenylsilyl chloride and a nonreductive debenzylation with the mild Lewis acid $BCl_3{\cdot}SMe_2$ complex,[15] furnished the (2*R*,3*R*)-4-(*tert*-butyldiphenylsilyloxy)-3-ethenyl-butan-1,2-diol (**15**).

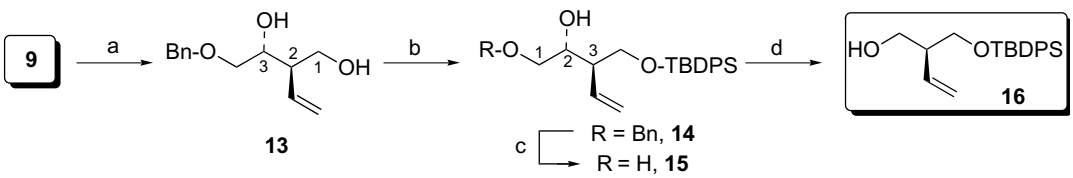
C-1 sacrifical oxidative cleavage, with $NaIO_4$ in H_2O/MeOH, followed by in situ reduction of the aldehyde with $NaBH_4$[16] afforded the key intermediate (*S*)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-but-3-en-1-ol (**16**) in good overall yield.

Similar results were obtained starting directly from the *cis*-epoxide **17**[17] (Scheme 4).

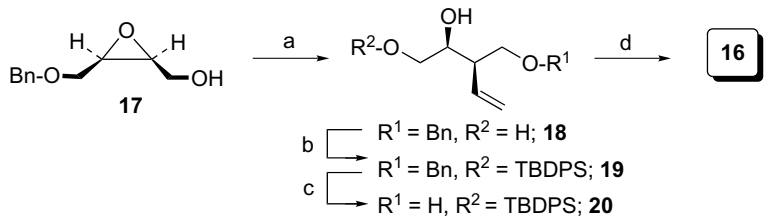
The two reaction sequences reported in Schemes 3 and 4 show that yields and enantiopurities were higher starting from the *cis*-epoxide **17** (52% overall yield, *e.e.*>98%[8]), compared with those starting from the *trans*-epoxide **9** (41% overall yield, *e.e.* = 98%[8]). Moreover the preparation of the *trans*-epoxide **9** requires the preliminary isomerisation of the (*Z*)-(benzyloxy)-2-buten-1-ol (**7**, see Scheme 1).



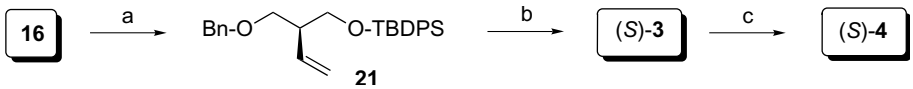
Scheme 2. (a) 1.5 equiv. of TBDMS-Cl, 2 equiv. of imidazole, DMF, 0°C, 2 h, 67%; (b) 0.2 equiv. of MABR, CH_2Cl_2, −78°C, 0.6 h.



Scheme 3. (a) (i) 3 equiv. of CH_2=CH-MgBr, 0.4 equiv. of CuI, Et_2O/THF (5:1), −10°C, 18 h; (ii) 1.0 equiv. of $NaIO_4$, THF/H_2O (1:1) 0°C, 4 h, 57%; (b) 1.5 equiv. of TBDPS-Cl, 1.0 equiv. of DMAP, CH_2Cl_2/pyridine (20:1), 0°C, 18 h, 96%; (c) 7 equiv. of $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 0°C, 2.5 h, 82%; (d) (i) 3.0 equiv. of $NaIO_4$, MeOH/H_2O (1:1), 0°C, 3 h; (ii) 3.0 equiv. of $NaBH_4$, MeOH, 0°C, 3 h, 92%.



Scheme 4. (a) (i) 3 equiv. of CH_2=CH-MgBr, 0.4 equiv. of CuI, Et_2O/THF (5:1), −10°C, 18 h; (ii) 1.0 equiv. of $NaIO_4$, THF/H_2O (1:1) 0°C, 4 h, 63%; (b) 1.5 equiv. of TBDPS-Cl, 1.0 equiv. of DMAP, CH_2Cl_2/pyridine (20:1), 0°C, 18 h, 96%; (c) 7 equiv. of $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 0°C, 2.5 h, 97%; (d) (i) 3.0 equiv. of $NaIO_4$, MeOH/H_2O (1:1), 0°C, 3 h; (ii) 3.0 equiv. of $NaBH_4$, MeOH, 0°C, 3 h, 88%.



Scheme 5. (a) 1.3 equiv. of BnBr, 1.1 equiv. of Ag_2O, CH_2Cl_2, rt, 48 h, 80%; (b) (i) O_3, MeOH/CH_2Cl_2 (1.7:1), −78°C, 0.4 h; (ii) Me_2S, 5 min; (iii) 8 equiv. of $NaBH_4$, −78°C→rt, 18 h, 93%; (c) 1.8 equiv. PDC, 4 Å ms, CH_2Cl_2, 95%.

Finally, protection of the free hydroxy group with benzyl bromide in presence of Ag_2O[18] and reductive ozonolysis with Me_2S/$NaBH_4$[19] furnished (*S*)-3-(benzyloxy)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-propan-1-ol (**3**) in 39% overall yield from **17** and *e.e.*>98%[8] (Scheme 5).[20] PDC oxidation[21] on (*S*)-**3** synthesised from the *cis*-epoxide **17** gave the expected (2*S*)-3-(benzyloxy)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-propanal (*S*)-**4** without any concurrent racemisation.[22]

In summary, we have reported the first enantioselective non-biological syntheses of stereodefined asymmetrised tris(hydroxymethyl)methane (THYM*) and bis(hydroxymethyl)acetaldehyde (BHYMA*). These methods provide a new straightforward access to their (*O*-benzyl, *O′*-silyl) derivatives with good chemical yields and excellent enantioselectivities.

Acknowledgements

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References

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8. The enantiomeric purity was checked through 400 MHz ^{1}H NMR Mosher's esters analyses (Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519) using C_6D_6 as solvent. These were carried out synthesising the two diastereomeric derivatives using (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-[(trifluoromethyl)phenylacetyl]chlorides ((*R*)-(−)- and (*S*)-(+)-MTPA-Cl) and integrating the relevant peaks in the ^{1}H NMR spectrum.
9. The organoaluminum-promoted rearrangement proceeds through an *anti* migration of the C-1 silyloxymethyl group towards the C-3 of the epoxide. Our result seems to confirm that silylated 2,3-epoxy alcohols not stabilising a transient positive charge on C-3 do not undergo the Yamamoto's rearrangement (see Ref. 6).
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17. (2*S*,3*R*)-(+)-3-Benzyloxy-2,3-epoxy-1-butyl 4-nitrobenzoate and its enantiomer are available from Fluka Chemie AG, Switzerland (*e.e.*>98%). Hydrolysis of the *p*-nitrobenzoate ester with 1% NaOH in MeOH gave the desired epoxy alcohol **17** in quantitative yield. See: Pettersson-Fasth, H.; Bäckvall, J.-E. *J. Org. Chem.* **1995**, *60*, 6091–6096. Epoxide **17** can also be synthesised through Sharpless asymmetric epoxidation[7a] in 84% yield and 90% *e.e.* (Mosher's esters ^{1}H NMR analyses).[8] It is possible to improve its enantiomeric purity (*e.e.*>98%) through recrystallisation of its 4-nitrobenzoate and subsequent hydrolysis.
18. Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3942–3943. Compound **21** is often contaminated by a 30–40% of the bis-benzyl ether.
19. Ozonolysis performed on batches containing less than 40–50 mg of **21** resulted in lower yields. When small amounts of **4** are requested, it is more convenient to obtain it by oxidation of the parent alcohol. Banfi, L.; Guanti, G.; Narisano, E. *Tetrahedron* **1993**, *49*, 7385–7392.
20. Selected data for compounds are as follows: **16**: $[\alpha]_D$ −17.5 ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (9H, s, $(CH_3)_3$C-Si), 2.27 (1H,bs, -O*H*), 2.55 (1H, m, H-2), 3.70–3.83 (4 H, m, -CH_2OH and -CH_2OTBDPS), 5.11 (1 H, dd, $J=17.7$, 1.0 Hz, C*H*H=CH-), 5.13 (1H, dd, $J=10.3$, 1.0 Hz, CH*H*=CH-), 5.69 (1H, m, CH_2=C*H*-), 7.43 (6H, m, C_6H_5-), 7.68 (4H, m, C_6H_5-); ^{13} C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.8 (×3), 47.6, 64.7, 66.0, 117.6, 127.7 (×4), 129.8 (×2), 133.1 (×2), 135.5 (×4), 135.8; HR EIMS *m*/*z* 340.1859 (calcd 340.1837 for $C_{21}H_{28}O_2Si$).
Compound **21**: $[\alpha]_D$ −5.1 ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s, $(CH_3)_3$C-Si), 2.58 (1H, m, H-2), 3.55 (1H, dd, $J=9.0$, 6.1 Hz, -C*H*HOBn), 3.65 (1H, dd, $J=9.0$, 6.3 Hz, -CH*H*OBn), 3.72 (1H, dd, $J=9.7$, 6.1 Hz, -C*H*HOTBDPS), 3.75 (1H, dd, $J=9.7$, 4.4 Hz, -CH*H*OTBDPS), 4.50 (2H, s, -CH_2Ph), 5.11 (1H, dd, $J=10.8$, 1.0 Hz, C*H*H=CH-), 5.12 (1H, dd, $J=17.7$, 1.0 Hz, CH*H*=CH-), 5.84 (1 H, m, CH_2=C*H*-), 7.30–7.45 (11H, m, C_6H_5-), 7.64 (4H, m, C_6H_5-); ^{13} C NMR (100 MHz, $CDCl_3$): δ 19.3, 26.8 (×3), 46.2, 64.1, 70.3, 73.1, 116.6, 127.4 (×7), 128.4 (×2), 129.5 (×2), 133.7 (×2), 135.6 (×4), 137.3, 138.5; HR EIMS *m*/*z* 430.2317 (calcd 430.2328 for $C_{28}H_{34}O_2Si$).
(*S*)-**3**: $[\alpha]_D$ −3.2 ($c=1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (9H, s, $(CH_3)_3$C-Si), 2.14 (1H, m, H-2), 2.68 (1H, bs, -O*H*), 3.62 (1H, dd, $J=9.3$, 6.7 Hz, -C*H*HOBn), 3.66 (1H, dd, $J=9.3$, 5.9 Hz, -CH*H*OBn), 3.80–3.85 (4H, m, -CH_2OTBDPS and -CH_2OH), 4.51 (2H, s, -CH_2Ph), 7.30–7.45 (11H, m, C_6H_5-), 7.68 (4H, m, C_6H_5-). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.8 (×3), 43.2, 63.4, 64.0, 70.0, 73.3, 127.6 (×7), 128.3 (×2), 129.7 (×2), 133.2 (×2), 135.5 (×4), 138.0; HR EIMS *m*/*z* 434.2265 (calcd 434.2277 for $C_{27}H_{34}O_3Si$).
(*S*)-**4**: $[\alpha]_D$ 8.3 ($c=0.8$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (9H, s, $(CH_3)_3$C-Si), 2.78 (1H, m, H-2), 3.82 (1H, dd, $J=9.4$, 6.2 Hz, -C*H*HOBn), 3.90 (1H, dd, $J=9.4$, 5.9 Hz, -CH*H*OBn), 4.04 (1H, dd, $J=10.4$, 2.6 Hz, -C*H*HOTBDPS), 4.07 (1H, dd, $J=10.4$, 5.4 Hz, -CH*H*OTBDPS), 4.47 (2H, s, -CH_2Ph), 7.30–7.45 (11H, m, C_6H_5-), 7.66 (4H, m, C_6H_5-); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.8 (×3), 54.5, 60.1, 65.8, 73.3, 127.5 (×3), 127.7 (×4), 128.3 (×2), 129.7 (×2), 133.0 (×2), 135.5 (×4), 138.0, 202.6; HR EIMS *m*/*z* 432.2117 (calcd 432.2121 for $C_{27}H_{32}O_3Si$).
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22. 400 MHz ^{1}H NMR Mosher's esters analysis, using C_6D_6 as solvent, on the alcohol derived from the $NaBH_4$ reduction of (*S*)-**4**, showed that no racemisation occurred during the oxidation and/or the work-up processes. The only other method known that avoids racemisation is a modification of the Swern oxidation.[19]