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Toward a Total Synthesis of an Aglycone of Spiramycin; Installation of the Hydroxy Groups at C-4 and C-5: a Model Study

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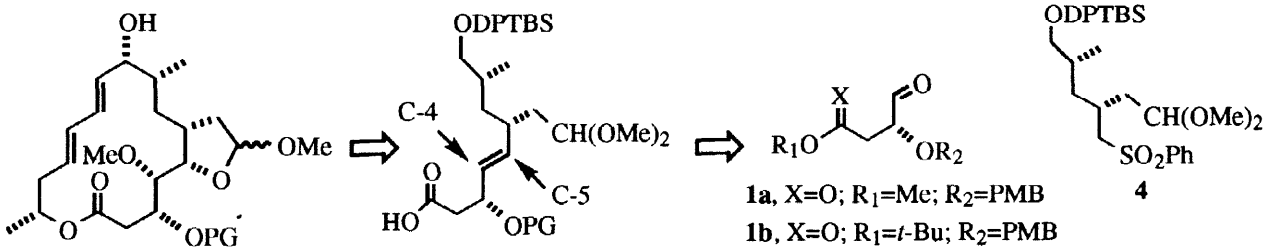
Abstract: *The stereochemical course of the osmium-mediated bis-hydroxylation of the allylic derivative* ***6c****, whose the structure is closely related to that of a C-1/C-7 fragment of the title aglycone, has been established unambiguously by X-ray analysis of a carboxylic acid derived from one of the two diastereomeric diols which formed.*

As we reported recently, due to the unstability of the aldehyde **1a**, attempted preparation of the fragment **2** of the aglycone **3** of spiramycin by a Julia-Paris-Kociensky (JPK) condensation of **1a** with the sulfone **4** proved unfeasible. This led us to prepare the related aldehydes **1b** and **1c**, which were expected to be more resistant than **1a** to the basic conditions of such an olefination reaction.[1]



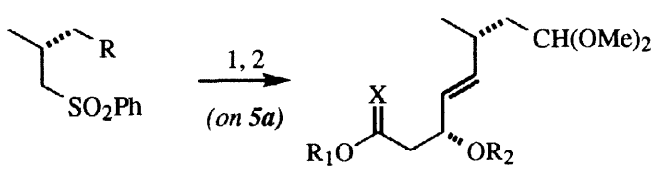
3 *(PG= protecting group)* **2**

1a, X=O; R_1=Me; R_2=PMB
1b, X=O; R_1=*t*-Bu; R_2=PMB
1c, X=H,H; R_1=C(O)-*t*-Bu; R_2=TBDMS

4

In order to define suitable conditions for executing the planned JPK coupling of the synthons **1b-c** with the sulfone **4** and, in the sequel, to get a precise insight on the stereochemical course of the ensuing osmium-mediated bis-hydroxylation step required to implement the oxygenated functionality at the C-4 and the C-5 positions, it appeared more judicious to perform first a model study by using the sulfone **5a**, which is easy to prepare[2] and whose substitution pattern is similar to that of the sulfone **4**. The results of this study are presented herein.

Addition of the aldehyde **1b** to a cooled (ca -78 °C) solution of the lithio derivative of the sulfone **5** in THF followed by an *in situ* acetylation with Ac_2O/DMAP gave a mixture of acetoxysulfones, which, by treatment with sodium amalgam, afforded the expected JPK product **6a** as a 3/1 mixture of *E* and *Z* isomers, respectively.



5a, R=$CH(OMe)_2$
5b, R=ODPTBS

6b-c (R_1, R_2, b and c as in **1**)

Reagents and conditions: 1- *i*) 2.3 M (in hexane) n-BuLi (1 eq.), THF (3 ml/mmol); -78 °C, 45 mn; *ii*) 0.3 M (in THF) **1b** (or **1c**) (1 eq.); -78 °C, 1 hour; *iii*) Ac_2O (2.1 eq.), DMAP (0.1 eq.); room t., 30 mn; 2-6% HgNa (3x5 eq.), 1/1 MeOH/AcOEt (20 ml/mmol); -50 °C, 4-8 hours, then 1/1 sat. aqueous KH_2PO_4/AcOEt (excess); 0 °C, 15 mn and extraction.

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The yield was low however (ca 30%), a result of the partial decomposition of the aldehyde **4b** as evidenced by the detection (NMR) of 4-methoxybenzyl alcohol. Pre-treatment of the lithiated sulfone with $BF_3.Et_2O$ or with $(i\text{-But})_2AlOMe$ failed to improve the yield. A better result was obtained by using the aldehyde **1c**, which was condensed with the sulfone **5** under the usual JPK-coupling conditions to give the unsaturated compound **6c** in 75%. Interestingly, that JPK product was essentially the pure *E* isomer.

Having overcame the difficulties presented by the olefination step, we next examined the osmium tetroxide-catalysed bis-hydroxylation of **6c**, our purpose being not only to find out optimal conditions with regards to the face-selectivity of this reaction, which, obviously, can deliver both diols ***S*-7** (presently desired) and ***A*-7**, but also to design the analytical tools permitting to determine accurately the structure of these products.

Accordingly, compound **6c** was submitted to classical *syn*-hydroxylation conditions (*i.e.* cat. OsO_4-NMO) to give a mixture of two bis-hydroxy compounds (^{13}C NMR), which proved to be (*vide infra*) ***A*-7** and ***S*-7**. Attempted fractionation of that crude product by chromatography was inefficient but, treatment of that diol mixture by methanol and PPTS afforded the four methyl-furanosides **8a**, that, to our delight, proved to have well-differentiated Rf in TLC on silica gel and could, accordingly, be separated by flash-chromatography.[3a]

Reagents and conditions: 1- *Classical conditions*: OsO4 (0.08 eq.), NMO (2 eq.), 9/1 acetone/water (5 ml/mmol); r.t., 12 hours; *Sharpless conditions*: AD-mix-α (or β) (1.4 g/mmol), $CH_3SO_2NH_2$ (1.5 eq.), $K_2OsO_4.2H_2O$ (0.06 eq.), 1/1 *t*-BuOH/H_2O (10 ml/mmol); r.t., 3 days; 2- PPTS (0.2 eq., 1/1 MeOH/CH_2Cl_2 (14 ml/mmol); r.t., 36 hours; 3- NaH (1.2 eq.), 1/1 MeI/DMF (3.3 ml/mmol); r.t., overnight.

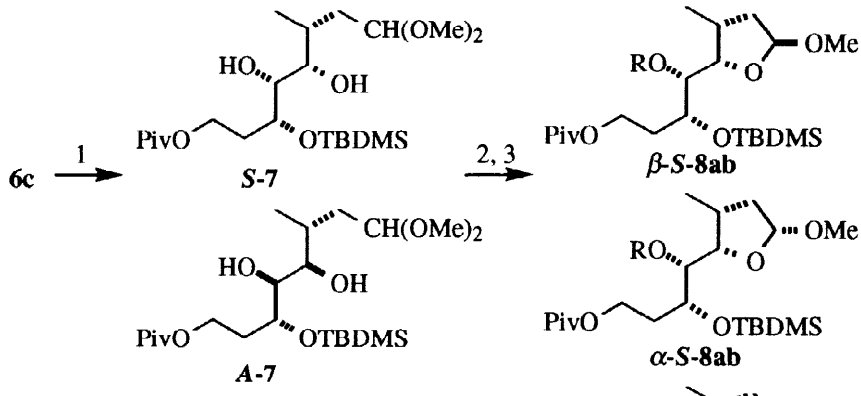


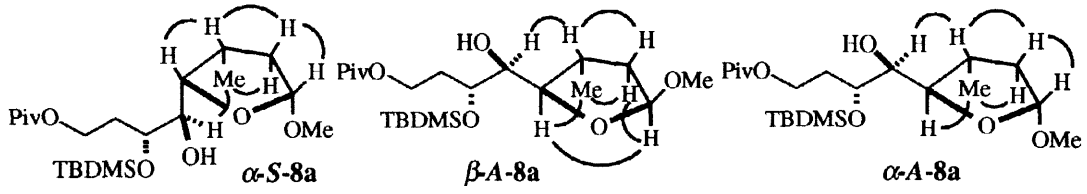
Table: Stereoselectivity of the OsO_4-mediated bis-hydroxylation of **6c**.

Oxidizing reagent	Composition of the mixture of acetals **8a** (%)*				***S*-7/*A*-7****	Yield (%)*
	***β*-S-8a**	***α*-S-8a**	***β*-A-8a**	***α*-A-8a**		
cat. OsO_4-NMO	5	31	34	30	2/3	82
AD-mix-α	11	49	22	18	3/2	70
AD-mix-β	–	08	53	39	1/10	79

* determined by weighing each pure isomer, after column-chromatography of the mixed-acetal mixture resulting from methanolysis of the crude osmylation product.
** (***β*-S*-8a+***α*-S*-8a)/(***β*-A*-8a+***α*-A*-8a)

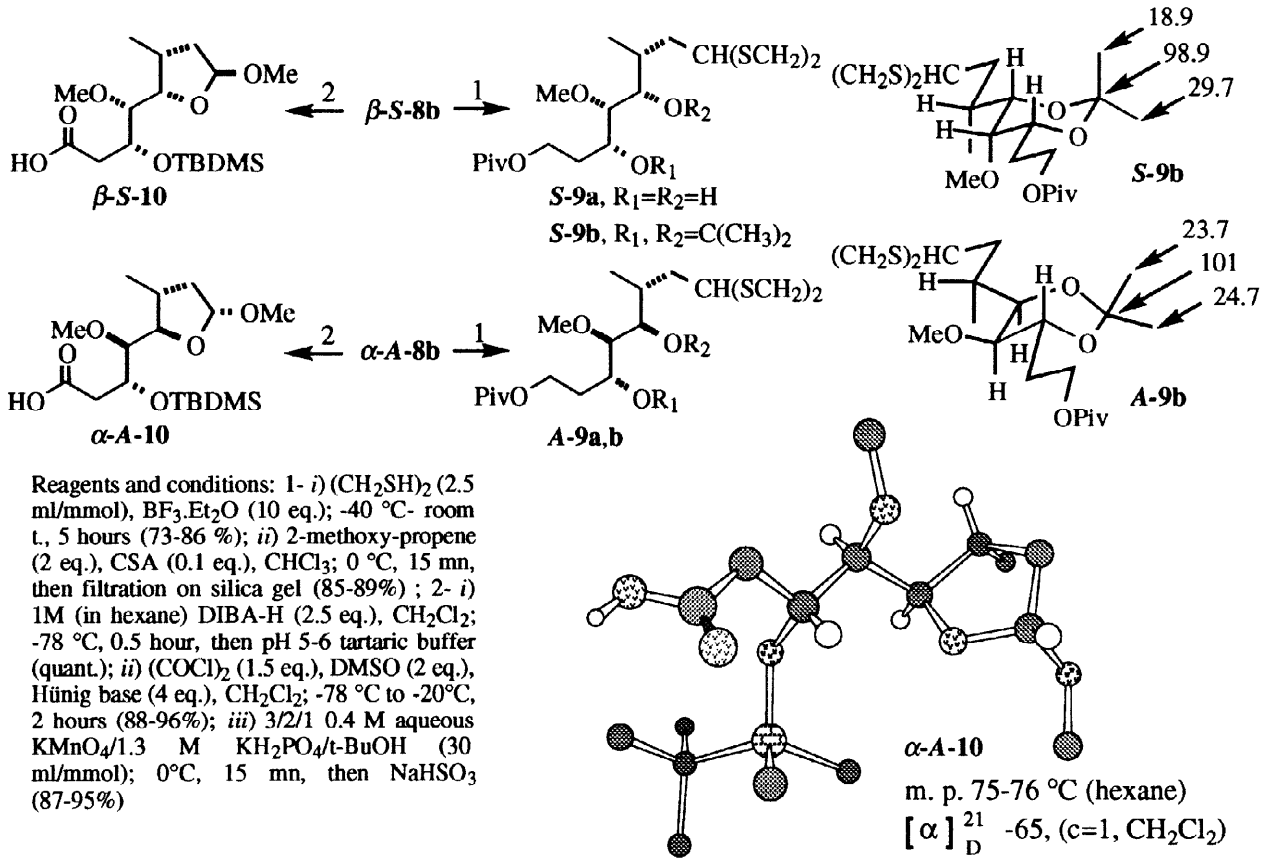
(a: R=H; b: R=Me)

Subsequent NMR analysis, especially NOE experiments, permitted, as shown below, to characterise each isomer, their ratio being established simply by weighing the relevant fractions (Table).[3b]



Confirmation of that structure assignment was obtained by reacting separately ***α*-A-8a** and ***β*-S-8a** with NaH and CH_3I in DMF, then with 1,2-ethanedithiol and $BF_3.Et_2O$ in chloroform. The 1,3-diols ***A*-9a** and **S-9a** that

formed, respectively, were reacted with 2-methoxy-propene and camphosulfonic acid to give the corresponding acetonide. The chemical shifts displayed in ^{13}C NMR by the geminated methyl groups and the quaternary carbon atom of the dioxopropane moiety of the single isomer which formed in both cases -*i.e.* **β-*A*-9b**, from **β-*A*-8a** and **β-*S*-9b**, from **β-*S*-8a**- are consonant with the indicated structure.[4] Finally, treatment of the mixed-acetals **α-*A*-8b** and **β-*S*-8b** by DIBA-H, in order to remove the pivaloyl protecting group, followed by a two-step oxidation (Swern reagent, then $KMnO_4$) afforded the acids **α-*A*-10** and **β-*S*-10**, respectively, the structure of the former being unambiguously established by X-ray analysis.[5]



Reagents and conditions: 1- *i*) $(CH_2SH)_2$ (2.5 ml/mmol), $BF_3.Et_2O$ (10 eq.); -40 °C- room t., 5 hours (73-86 %); *ii*) 2-methoxy-propene (2 eq.), CSA (0.1 eq.), $CHCl_3$; 0 °C, 15 mn, then filtration on silica gel (85-89%) ; 2- *i*) 1M (in hexane) DIBA-H (2.5 eq.), CH_2Cl_2; -78 °C, 0.5 hour, then pH 5-6 tartaric buffer (quant.); *ii*) $(COCl)_2$ (1.5 eq.), DMSO (2 eq.), Hünig base (4 eq.), CH_2Cl_2; -78 °C to -20°C, 2 hours (88-96%); *iii*) 3/2/1 0.4 M aqueous $KMnO_4$/1.3 M KH_2PO_4/t-BuOH (30 ml/mmol); 0°C, 15 mn, then $NaHSO_3$ (87-95%)

α-*A*-10
m. p. 75-76 °C (hexane)
$[\alpha]_D^{21}$ -65, (c=1, CH_2Cl_2)

The predominant formation of ***A*-7** by bis-hydroxylation of **6c** could be anticipated in view of the model suggested by Kishi[6a] for the OsO_4-NMO oxydation of related allylic derivatives. Application of the more elaborated model of Sharpless[6b] to **6a** showed that the use of the AD-mix-α reagent would favour in some extent the formation of the desired diol ***S*-7** as observed effectively (Table). The more spectacular effect was recorded by using AD-mix-β however, in which case the isomer ***A*-7** was formed with a fairly good selectivity.

In conclusion, the aldehyde **1c** proved to condense efficiently with the sulfone **5** to give the olefin **6c** as the pure *E* isomer. The ensuing osmium-mediated bis-hydroxylation of **6c** proceeded with an imperfect selectivity, giving an unseparable mixture of the two possible diastereomeric diols ***S*-7** and ***A*-7**. Fortunately, treatment of that mixture by methanol furnished the corresponding mixed-acetals **8a**, which could be efficiently fractionated and accurately characterised by NMR. Finally, the possibility to convert the protected primary hydroxy group at C-1 of these acetals into a carboxylic acid functionality has been substantiated. Hence these results pave the way for a convenient conversion of the sulfone **4** into the acid **2**, which is an essential part of our planned synthesis of the aglycone **3** of spiramycin. Results along this line will be reported in due course.

Acknowledgement: Thanks are due to Rhône-Poulenc Rorer for a grant (to G.O.).

References and Notes

1- Breuilles. P.; Oddon, G.; Uguen, D. *Tetrahedron Letters* **1997**, *38*, 6607-6610.

2- The sulfone **5b** (Schmittberger, T; Uguen, D. *Tetrahedron Letters* **1997**, *38*, 2837-2840) was reacted sequentially with TBAF in THF, TosCl in pyridine, KCN in DMSO, DIBA-H in CH_2Cl_2, and $CH(OMe)_3$/CSA in MeOH to give **5a** (33% overall Yield; $Bp_{0.1}$ 180 °C; ^{13}C NMR: 20.52, 25.51, 39.09, 52.64, 53.1, 62.3, 102.74, 127.97, 129.33, 133.62, 140.13; $[\alpha]_D$ -7 (c=2.6).

3- a) Rf values (eluant: 95/5 hexane/AcOEt; 6 elutions): *α-S*-**8a**: 0.46; *β-A*-**8a**: 0.4; *β-S*-**8a**: 0.26; *α-A*-**8a**: 0.18; b) Whereas distinctive NOE correlations were observed for *α-S*-**8a**, and *α-A*-**8a**, that recorded for the isomer *β-S*-**8a** were not so conclusive. *Selected data*: **6c**: C 64.34 (calc. 64.27), H 7.33 (calc. 7.19); ^1H NMR: -0.05 (s, 3H), -0.04 (s, 3H), 0.8 (s, 9H), 0.93 (d, J=6.6 Hz, 3H), 1.12 (s, 9H), 1.45-1.8 (m, 4H), 2.15-2.3 (m, 1H), 3.2 (s, 3H), 3.22 (s, 3H), 4.03 (t, J=6.3 Hz, 2H), 4.05-4.15 (m, 1H), 4.28 (t, J=5.7 Hz, 1H), 5.3-5.4 (m, 2H); ^{13}C NMR: -4.9, -4.1, 18.2, 20.7, 25.9, 27.3, 32.6, 37.5, 38.67, 39.29, 52.42, 52.62, 61.1, 70.47, 103, 131.9, 136, 178.3; $[\alpha]_D$ -2 (c=2.3); *S*-**7**: ^{13}C NMR: -4.51, -4.22, 14.08, 18.07, 25.91, 27.28, 32.04, 32.95, 36.64, 38.79, 52.64, 52.94, 60.89, 70.07, 72.35, 73.73, 103.19, 178.42; *A*-**7**: ^{13}C NMR: -4.68, -4.53, 17.08, 18.04, 25.88, 27.25, 32, 32.24, 35.53, 38.75, 52.74, 60.88, 71.76, 72.41, 73.93, 103.33, 178.52; *α-S*-**8a**: m.p. 47 °C; ^1H NMR: 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.12 (d, J=6.7 Hz, 3H), 1.19 (s, 9H), 1.68 (ddd, J=13.3, 9.3, 3.9 Hz, 1H), 1.75-1.86 (m, 1H), 1.92-2.02 (m, 1H), 2.28-2.36 (m, 1H), 2.37-2.46 (m, 1H), 3.29 (d, J=10.3 Hz, 1H, O*H*), 3.43 (s, 3H), 3.49 (ddd, J=10.3, 5.1, 1.5 Hz, 1H), 3.82-3.88 (m, 1H), 4.02-4.09 (m, 1H), 4.24-4.3 (m, 1H), 4.33 (dd, J=7.5, 1.5 Hz, 1H), 5.02 (dd, J=6.1, 3.9 Hz, 1H); $[\alpha]_D$ +10 (c=0.5); *β-A*-**8a**: ^1H NMR: 0.08 (s, 6H), 0.88 (s, 9H), 1.04 (d, J=6.6 Hz), 1.19 (s, 9H), 1.6 (ddd, J=12.8, 11, 5.1 Hz, 1H), 1.95-2.05 (m, 2H), 2.09 (dd, J=12.8, 7.3Hz, 1H), 2.35-2.5 (m, 1H), 2.71 (d, J=8.6 Hz, 1H, O*H*), 3.27 (t, J=8.2 Hz, 1H), 3.34 (s, 3H), 3.75 (dt, J=8, 4.9 Hz, 1H), 3.91 (d, J=8 Hz, 1H), 4.15-4.3 (m, 2H), 4.91 (d, J=4.9 Hz, 1H); $[\alpha]_D$ +18 (c=1); *β-S*-**8a**: ^1H NMR: 0.09 (s, 6H), 0.89 (s, 9H), 1.05 (d, J=7 Hz, 3H), 1.19 (s, 9H), 1.7-1.85 (m, 1H), 1.9-2.05 (m, 1H), 2.39 (d, J=8.3 Hz, 1H, O*H*), 2.45-2.55 (m, 1H), 3.34 (s, 3H), 3.35-3.45 (m, 1H), 3.5-3.6 (m, 1H), 3.74 (dd, J=8.7, 1.4 Hz, 1H), 4.05-4.35 (m, 1H), 5.04 (dd, J=5.1, 1.8 Hz, 1H); $[\alpha]_D$ +65 (c=1); *α-A*-**8a**: ^1H NMR: 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.04 (d, J=6.8 Hz, 3H), 1.18 (s, 9H), 1.48 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (d, J=8.6 Hz, 1H, O*H*)), 2.34 (ddd, J=13.4, 5.8, 5.6 Hz, 1H), 3.33 (s, 3H), 3.37 (t, J=7.4 Hz, 1H), 3.74 (dd, J=8.7, 1.4 Hz, 1H), 3.78-3.83 (m, 1H), 4.1-4.18 (m, 1H), 4.24-4.31 (m, 1H), 5 (dd, J=5.8, 3.1 Hz, 1H); $[\alpha]_D$ -60 (c=1); *S*-**9b**: ^{13}C NMR: 14.91, 18.92, 27.31, 29.72, 31.14, 34.11, 38.36, 38.55, 38.82, 42.16, 51.57, 60.96, 61.36, 69.64, 74.99, 76.65, 98.91, 178.54; *A*-**9b**: ^{13}C NMR: 15.76, 23.7, 24.74, 27.3, 32.21, 34.79, 38.25, 38.83, 43.22, 52.2, 58.7, 60.97, 70.06, 75.32, 82.46, 100.97, 178.58; *α-A*-**10**: m. p. 75-76 °C; C 56.2 (calc. 56.32), H 9.25 (calc. 9.45); $[\alpha]_D$ -65 (c=1). ^1H and ^{13}C NMR spectra: 400 and 50 MHz, respectively, $CDCl_3$; $[\alpha]_D$: 21 °C, CH_2Cl_2.

4- Cieplak, P.; Howard, A. E.; Powers, J. P.; Rychnovsky, S. D.; Kollman, P. A. *J. Org. Chem.* **1996**, *61*, 3662-3668.

5- Crystal data for *α-A*-**10** : $C_{17}H_{34}O_6Si$, M.W. = 362.5, orthorhombic, space group $P2_12_12_1$, a = 6.844(2), b = 11.593(3), c = 26.107(7) Å , U = 2071.6 $Å^3$, Z = 4, dcalc = 1.162 gcm^{-3}, μ (MoKα) = 1.333 mm^{-1}. Data were collected at room temperature using graphite monochromated MoKα radiation (λ = 0.7107 Å) on a Nonius-CAD4-F diffractometer and a crystal of dimensions 0.38*0.32*0.32 mm^3. 2466 reflections were collected ($2° < \theta < 26°$). 1597 were unique with $I>3\sigma(I)$. Absorption corrections from the psi scans of 4 reflections were applied. The structure was solved using direct methods and refined against |F| (full matrix, $\sigma^2(F^2) = \sigma^2_{counts} + 0.0064\ F^4$). Hydrogen atoms were introduced as fixed contributors (C-H = 0.95 Å, B(H)=1.3*Beqv of attached C). The absolute configuration was determined by refining Flack's parameter. Final results : R(F) = 0.040, Rw(F) = 0.059, GOF = 1.181, largest residues in final difference map = +0.20/-0.16 $eÅ^{-3}$. For all computations the Nonius OpenMolen Package (Fair, C.K. in MolEN. An Interactive Intelligent System for Crystal Structure Analysis. Enraf-Nonius, Delft, The Netherlands, 1990) on a DEC Alpha 3600S computer was used.

6- a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron*, **1984**, *40*, 2247-2255; b) Kolb, H. C.; VanNieuwenzhe, M. S.; Sharpless K. B. *Chem. Reviews* **1994**, *94*, 2483-2547.