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Intramolecular asymmetric Pummerer reactions as a key step in the synthesis of bicyclic precursors of anthracyclinones†

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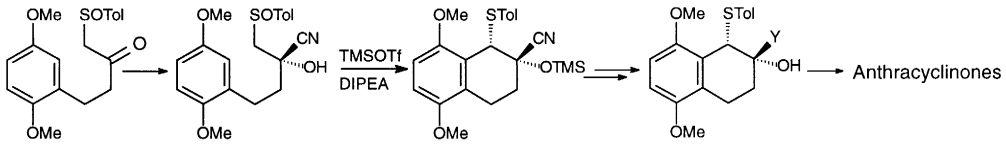
Abstract

Highly stereoselective Pummerer reactions were observed on reaction of β-hydroxysulfoxides **2a**–**2d** and **2′b** with TMSOTf. Sulfenium intermediates are captured intramolecularly by the electrophilic aromatic ring, thus yielding bicyclic structures with a *p*-tolylsulfenyl group at the benzylic position in a *cis* arrangement with respect to the hydroxyl group. The stereogenicity transfer seems to be mainly controlled by the hydroxylated chiral carbon. Resulting compounds **3a**, **3c** and **3d** can be used as bicyclic precursors of different anthracyclinones.

Considerable attention has been paid to the Pummerer reaction as a synthetically useful process.[1] Besides acetic anhydride, or the more electrophilic trifluoroacetic anhydride, other useful promoters of these reactions are trimethylsilyl trifluoromethanesulfonate (TMSOTf) and *O*-silylated ketene acetals, which allow the reactions to be carried out at lower temperatures. The intramolecular capture of the thionium ion by aromatic rings, a Friedel–Crafts-like process, has been used to prepare polycyclic ring systems.[2] The asymmetric Pummerer reaction of optically active sulfoxides has also been investigated,[3] with the *O*-silylated ketene acetals being the best promoters.

In the course of our studies directed towards the preparation of optically pure anthracyclinones,[4] the bicyclic compounds **4**, precursors of the desired tetracyclic system, were obtained from **3a**. This thioether was obtained in a highly stereoselective manner, by intramolecular capture of the thionium ion generated



1 **2a** **3a** (80% de) **4** (Y=CHO, CH_3, Et, COMe)

Scheme 1.

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† In memory of Professor J. de Pascual Teresa.

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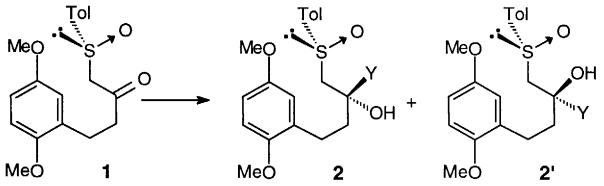
when optically pure β-hydroxy-β-cyano sulfoxide **2a** was treated under Pummerer conditions (Scheme 1). As a promoter of this reaction we used TMSOTf and DIPEA[5] (di-isopropylethylamine) instead of Ac_2O or $(CF_3CO)_2O$ to avoid the competition between the nucleophilic counterion (TfO^-) and the aromatic ring for the Pummerer intermediate.

The cyano group of **3a** was transformed into $COCH_3$, methyl, ethyl and other groups, which are usually present in the natural anthracyclinones, but some of these transformations required the use of sequences longer than expected.[4] This prompted us to investigate the cyclization of other enantiomerically pure sulfinyl derivatives, which could be more easily transformed into the typical substituents at C-9 of anthracyclinones. Additionally, the high stereoselectivity observed in the synthesis of **3a** (80% de), suggested that an efficient intramolecular asymmetric Pummerer rearrangement was taking place which deserved a more detailed study. In this paper we describe the results obtained in the intramolecular asymmetric Pummerer reaction of enantiomerically pure β–hydroxysulfoxides **2a**–**2e** and **2′b** (Table 1) when they are treated with TMSOTf and DIPEA to give their corresponding benzylthioethers **3a**–**3e** and **3′b**.

Table 1
Reaction conditions for the synthesis of compounds **2** and **2′**

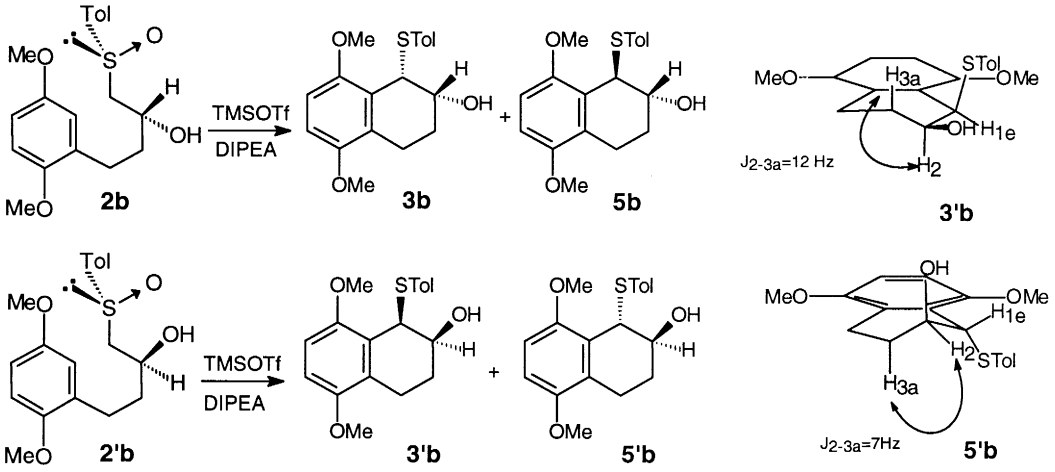


Entry	Reagent	Solvent/T°C	Time	Y	2/2'	Yield[b]
1	Et_2AlCN	THF/-40	0.5 hr	CN (**a**)	>98/2	97%
2	DIBAL-H	THF/-78	3 hr	H (**b**)	4/96	89%[c]
3	DIBAL-H/ $ZnBr_2$[a]	THF/-78	3 hr	H (**b**)	>98/2	98%
4	HCCMgBr/$ZnBr_2$[a]	Toluene/rt	1 hr	HCC (**c**)	90/10	60%
5	$H_2CCHMgBr/ZnBr_2$[a]	Toluene/-78	4 hr	H_2C=CH (**d**)	86/16	60%
6	$Me_3Al/ZnBr_2$[a]	CH_2Cl_2/rt	1 hr	CH_3 (**e**)	85/15	64%

a) 3 eq of $ZnBr_2$ were used, b) Isolated yield of major isomer, c) Separation of the mixture **2b**+**2'b** was not possible.

The synthesis of **2a** (entry 1, Table 1) has been previously reported.[4] Compounds **2b** and **2′b** were prepared by highly stereoselective reduction of **1**[4] with DIBAL-H and DIBAL-H/$ZnBr_2$, respectively (Table 1, entries 2 and 3). DIBAL-H reduction[6] yielded a 4:96 mixture of **2b** and **2′b** that are epimers at the hydroxylic carbon (89% yield). Compound **2b** was obtained as the sole diastereoisomer by treatment of **1** with DIBAL-H/$ZnBr_2$.[7] Reactions of **1** with ethynyl and vinyl Grignard reagents (entries 4 and 5, Table 1) were carried out following the previously described conditions.[8] Ethynyl magnesium bromide yielded a 90:10 mixture of the two possible carbinols, **2c** and **2′c**, whereas reaction with the vinyl derivative resulted in a 84:16 mixture of epimers **2d** and **2′d**. These mixtures were easily separated by chromatography. The isolated yields of the major diastereoisomers, **2c** and **2d**, were 60 and 55%, respectively. Finally, compound **2e** (entry 6, Table 1) was the major component of the 85:15 readily separated mixture obtained from the reaction of **1** with $Me_3Al/ZnBr_2$, under previously reported conditions.[9] The absolute configurations of the carbinols indicated in Table 1, were assigned on the basis of the well-established stereochemical course of the corresponding reactions of reduction,[6] hydrocyanation,[10] and alkylation,[8,9] taking into account that the configuration at sulfur in the starting sulfoxides is not affected by the conditions used.

The Pummerer reactions of **2a**–**2e** and **2′b** were studied using TMSOTf (4.5 equiv.) and DIPEA (4.5 equiv.). The reaction of **2b** at room temperature yielded a 8:1 mixture of the two cyclized products, **3b** and **5b**,[11] epimers at the benzylic carbon (Scheme 2), which were easily separated by chromatography. The major product was isolated in 81% yield. When the reaction was carried out at 0°C, compound **3b** was formed exclusively. Under similar conditions, the 96:4 mixture of **2′b** and **2b** yielded a 7:3 mixture of **3′b** and **5′b** at room temperature but only **3′b** (92% ee) at 0°C. Compounds **3b** and **3′b**, which exhibited identical physical and spectroscopic features, showed the opposite sign of optical rotation which proves that they are enantiomers (Scheme 2). The same behaviour was observed for **5b** and **5′b**. The stereochemistry of these compounds was established (Scheme 2) from their ^{1}H NMR parameters. As the STol group must adopt a pseudoaxial arrangement in order to avoid allylic strain with the OMe group, the main difference between compounds **3′b** and **5′b** (or **3b** and **5b**) is the axial or equatorial arrangement of H-2, easily deduced from its vicinal coupling constant with H-3a. Compounds **3b** and **3′b**, the major components of their respective reaction mixtures, have a *cis*-relationship between the OH and STol groups, whereas it is *trans* for the minor isomers, **5b** and **5′b**. These results demonstrate that the configuration induced at the benzylic carbon is related to that of the hydroxylic carbon of the starting sulfoxide (*R* from **2b** and *S* from **2′b**) and is independent of the configuration of the sulphur.

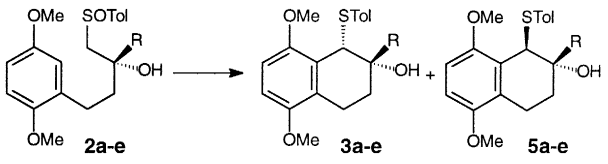


Scheme 2.

The reaction of **2a** with TMSOTf and DIPEA at 0°C yielded a 9:1 mixture of **3a** and **5a**.[4] Optically pure **3c** was only formed from **2c** (Table 2), but partially racemized **3c** (80% ee) was obtained from a 9:1 mixture of **2c** and **2′c**. This last reaction required 1 hour to complete, a longer reaction time than for the above-mentioned reactions of **2a**, **2b** and **2′b** (30 min). After 90 min, the reaction of **2d** yielded a 1:1 mixture of **3d** and **6d**, which remained unaltered with time. Compound **6d** was characterized

Table 2
Cyclization reaction of β-ketosulfoxides **2a**–**e** with TMSOTf/DIPEA

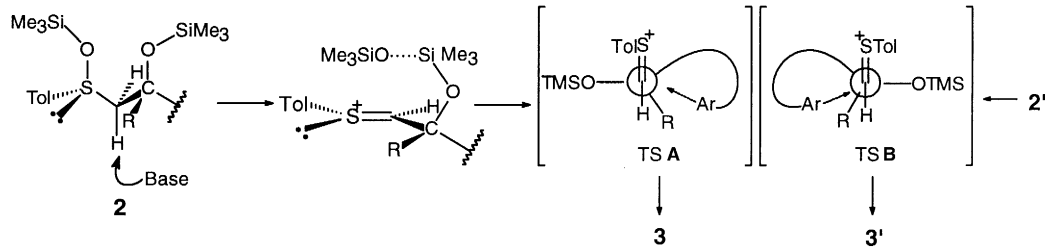
Compound	T (°C)	t (min)	**3/5**	Yield
2a	0	30	9/1	98%
2b	0	30	1/-	81%
2c	0	60	1/-	60%
2d	0-rt	90	1/-	50%
2e	rt	120	-	-[13]



as the trimethylsilyl derivative of the starting carbinol **2d**.[12] After 2 hours at rt, reaction of **2e** with TMSOTf–DIPEA did not afford the expected bicyclic compound (an acyclic thioether was exclusively formed[13]). These results suggest that increasing the size of the R group in the starting hydroxysulfoxide makes the intramolecular capture of the Pummerer intermediate by the aromatic ring more difficult.

The absolute configuration of compounds **3a**, **3c**–**e**[13] was established from the *cis*-relationship between their STol and OH groups which was deduced from their ^{13}C NMR spectra[14,15] assuming that the known configuration at the hydroxylic carbons is not affected by the reaction conditions.

The configuration induced at the benzylic carbon is *S* for all compounds of Table 2, allowing the OH and STol group to become *cis*. The sulfinyl configuration has no significant influence on the stereochemical course of the reactions, which suggests that the formation of intimate ion pairs between the sulfenium ion and the Me_3SiO^- counterion (which would block one of the faces of the sulfenium intermediate to the attack of the nucleophile[16]) must be excluded.



Scheme 3.

As the deprotonation step proceeds through an E2-type elimination, the formation of the *anti*-sulfenium intermediate would be favoured from steric grounds (see Scheme 3). We postulate formation of the free sulfenium ion,[17] which evolves into the bicyclic compounds by an intramolecular attack of the nucleophilic ring. This attack takes place according to the Felkin–Anh model of Cram's rule (Scheme 3). The OTMS (perhaps associated with the $TMSO^-$ counterion[17]) adopts the orthogonal arrangement with respect to the $C{=}S^+$ bond. The favoured TS for diastereoisomers **2** and **2′**, which makes the trajectory of the attacking nucleophile coincident with that of Dunitz's rule,[18] will be **A** and **B**, respectively (Scheme 3), both yielding compounds with the STol and OTMS in a *cis* arrangement. This model would also explain why the reactivity decreases on increasing the size of the R group.

Acknowledgements

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11. The products can be isolated as alcohols or their OTMS derivatives, depending on the conditions used for their isolation (Ref. 4).
12. Trimethylsilyl derivatives were isolated in all cases instead of the starting alcohols when the reactions were stopped before completion, thus suggesting they are formed before the Pummerer reactions.
13. The reaction of the TMSO derivative of **2e** with TFAA afforded a complex reaction mixture containing **3e** (10% isolated yield).
14. Compound **3b** [1*S*,2*R*]: $[\alpha]_D^{20}$=+293.2 (*c* 0.76 $CHCl_3$). ^{1}H NMR (500 MHz) δ: 7.50, 7.10 (AA′BB′, *J*=8.06 Hz, 4H), 6.70 (s, 2H), 4.74 (dd, *J*=4.4, 1.8 Hz, 1H), 4.04 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 2.96 (ddd, *J*=18.25, 6.35, 1.35 Hz, 1H), 2.61 (d, *J*=11.1 Hz, 1H, OH) 2.57 (ddd, *J*=18.6, 12.25, 6.9, 1H), 2.36 (s, 3H), 2.0 (m, 1H), 1.93 (cd, *J*=12.35, 6.4 Hz, 1H). ^{13}C NMR (75 MHz) δ: 151.15, 150.95, 136.75, 133.88, 131.66, 129.46, 126.63, 125.56, 108.47, 107.68, 69.14, 55.26, 55.45, 53.25, 27.71, 23.15, 21.02. Compound **3′b** [1*R*,2*R*]: ^{1}H NMR (500 MHz) δ: 7.49, 7.15 (AA′BB′, *J*=8.08 Hz, 4H), 6.74 (s, 2H), 4.50 (t, *J*=2.35 Hz, 1H) 4.26 (m, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 2.86 (ddd, *J*=18.3, 7.1, 1.75, 1H), 2.69 (ddd, *J*=18.3, 12.05, 6.8, 1H), 2.54 (*J*=12.1, 7.05, 2.0 Hz, 1H), 2.37 (s, 3H), 1.95 (m, 1H), 1.57 (s_{bs}, 1H, OH). ^{13}C NMR (75 MHz) δ: 152.24, 150.93, 137.27, 132.57, 132.43, 129.62, 126.22, 122.56, 108.71, 107.98, 68.04, 55.93, 55.55, 47.90, 22.86, 21.07, 17.42. Compound **3a** $[\alpha]_D^{20}$=+288.6 (*c* 0.5 $CHCl_3$). ^{1}H NMR δ: 7.46, 7.07 (AA′BB′, *J*=8.04 Hz, 4H), 6.69 (s, 2H), 4.96 (d, *J*=2.3 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 2.74 (m, 2H), 2.33 (s, 3H), 2.16 (m, 2H). ^{13}C NMR (75 MHz) δ: 150.79, 150.62, 136.79, 133.69, 132.05, 129.15, 123.88, 123.43, 120.70, 108.98, 108.23, 72.00, 55.72, 55.41, 53.57, 29.75, 22.11, 21.29, 1.09. Compound **3c** $[\alpha]_D^{20}$=+348.3 (*c* 0.6 $CHCl_3$). ^{1}H NMR δ: 7.51, 7.11 (AA′BB′, *J*=8.1 Hz, 4H), 6.68 (s, 1H), 4.80 (d, *J*=1.8 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.11 (s, 1H, OH), 3.1–2.8 (m, 2H), 2.33 (s, 3H, CH_3), 2.30 (s, 1H), 2.15 (m, 2H). ^{13}C NMR δ: 150.8 (2C), 137.2, 133.1, 131.9, 129.7, 125.7, 125.0, 108.5, 107.7, 84.0, 72.7, 69.0, 56.9, 55.5, 31.8, 22.7, 21.0. Compound **3d** $[\alpha]_D^{20}$=+138.3 (*c* 0.6 $CHCl_3$). ^{1}H NMR δ: 7.40, 7.01 (AA′BB′, *J*=8.17 Hz, 4H), 6.60 (s, 2H), 5.90 (dd, *J*=17.30, 10.65 Hz, 1H), 5.24 (dd, *J*=17.30, 1.56 Hz, 1H), 5.00 (dd, *J*=10.65, 1.56 Hz, 1H), 4.66 (d, *J*=2.4 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.59 (m, 2H), 2.30 (s, 3H), 1.98 (m, 2H), 1.55 (s, 1H, OH), 0.7(s, 9H). ^{13}C NMR δ: 150.9, 150.6, 141.0, 135.5, 131.2, 128.7, 127.0, 124.8, 114.4, 107.9, 107.7, 55.8, 55.7, 55.6, 53.79, 29.3, 22.6, 21.0, 2.45. Compound **3e** $[\alpha]_D^{20}$=+174 (*c* 0.1 $CHCl_3$). ^{1}H NMR δ: 7.48, 7.11 (AA′BB′, *J*=8.1 Hz, 4H), 6.66 (s, 1H), 4.42 (d, *J*=2.2 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.93 (ddd, *J*=18.53, 6.68, 1.3 Hz, 1H), 2.51 (m, 1H), 2.33 (s, 3H, CH_3), 1.98 (m, 1H), 1.80 (m, 1H), 1.57 (s_{bs}, 1H, OH), 1.23 (s, 3H). ^{13}C NMR δ: 151.18, 151.04, 136.79, 134.03, 131.55, 129.48, 127.34, 124.52, 108.15, 107.62, 70.50, 58.06, 55.52, 55.47, 32.54, 23.56, 22.78, 21.05.
15. According to the influence of the substituents at C-2 on the chemical shifts of C-4 (see: Eliel, E.; Wilen, S.H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, 1994, pp. 717) the $\delta_{C\text{-}4}$ values observed for **3a** and **3c**–**e** (22–22.6 ppm) suggest they must exhibit the same configuration as **3b** ($\delta_{C\text{-}4}$=23.19 ppm) with STol and OH in a *cis* arrangement, but different from **5b** ($\delta_{C\text{-}4}$=17.40 ppm).
16. In these cases, the configuration of the sulfoxides is the main controller of the stereoselectivity of the Pummerer rearrangement. See: Kita, Y.; Shibata, N.; Fukui, S.; Bando, M.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1763, and Ref. 3.
17. This could be justified by association of the $TMSO^-$ ion to the other OTMS group present in the molecule. This interaction has been previously invoked (Shibata, N.; Fujita, S.; Gyoten, M.; Matsumoto, K.; Kita, Y. *Tetrahedron Lett.* **1995**, *36*, 109).
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