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Convenient preparation of carbonyl compounds from 1,2-diols utilizing Mitsunobu conditions

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Abstract

1,1-Disubstituted 1,2-diols are efficiently converted into carbonyl compounds by reaction with triphenylphosphine and diethyl azodicarboxylate.

Keywords: Mitsunobu reactions; diols; aldehydes.

The Mitsunobu reaction is a useful synthetic tool which allows the conversion of an alcohol function into a wide variety of functional groups.[1–8]

$$\mathrm{ROOC{-}N{=}N{-}COOR + Ph_3P + R'OH + Nu: \rightarrow Nu\text{-}R' + Ph_3PO + ROOC{-}NH{-}NH{-}COOR}$$

Cyclic compounds are formed when the alcohol molecule contains a suitably placed nucleophile. Epoxides are obtained from acyclic 1,2-diols under the Mitsunobu conditions[9] and from cyclic *trans*-1,2-diols.[10–13] Under the same conditions triphenylphosphoranes resulted from cyclic *cis*-1,2-diols.[11–14] Methyl shikimate (**8a**), having *cis*- and *trans*-diol groups, leads to the corresponding epoxide **8b**, under these conditions.[15]

During our research on the synthesis of bioactive compounds from labdane diterpenes we have found that diol **12a** is transformed with excellent yield into drimenal (**12b**)[16] when it is treated with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) in benzene. In order to elucidate the scope and synthetic application of this reaction the behaviour of a variety of 1,2-diols with these reagents has been studied. The results obtained are summarized in Table 1 and compared with those previously reported. As may be seen, monosubstituted and disubstituted 1,2-diols are converted into epoxides or phosphoranes, depending on whether the hydroxyl groups adopt an antiperiplanar (cyclic *trans*-diols and acyclic diols) or an eclipsed conformation (*cis*-diols), respectively. The formation of phosphorane **3b** from diol **3a** can be attributed to the bulky dioxolane groups which prevent the hydroxyl groups from adopting the *anti* disposition. 1,1-Disubstituted-1,2-diols lead to the formation of aldehydes or ketones, depending on whether the less substituted carbon is primary or secondary. Even acyclic 1,1-disubstituted

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Table 1
Reactions of 1,2 diols with the TPP–DEAD system

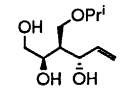
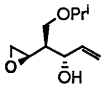
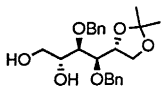
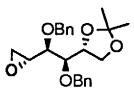
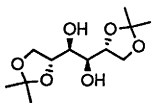
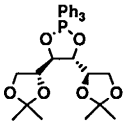
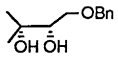
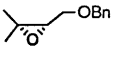
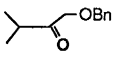
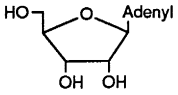
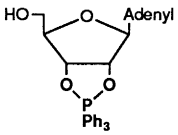
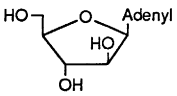
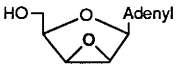
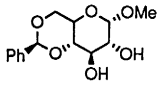
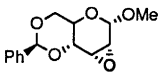
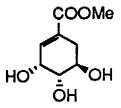
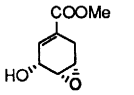
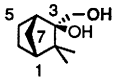
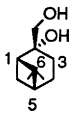
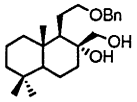
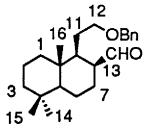
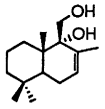
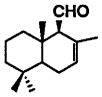
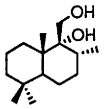
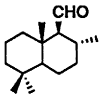
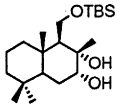
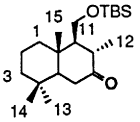
Diol	Conditions	Product	References
 **1a**	Benzene, Molecular sieves, 80°C, 14h	 (85%) **1b**	(9)
 **2a**	Benzene, rt, 2h	 (90%) **2b**	
 **3a**	Benzene, rt, 2h 45 min	 (95%) **3b**	
 **4a**	Benzene, rt, 4h	 **4b** (75%)  **4c** (15%)	
 **5a**	Dioxane, 70°C, 40 min	 (72%) **5b**	(12)
 **6a**	Dioxane, 70°C, 40 min	 (90%) **6b**	(12)
 **7a**	Dioxane, 110°C 45 min	 (87%) **7c**	(13)

Table 1 (continued)

Diol	Conditions	Product	References
 **8a**	THF, rt, 1h	 (77%) **8b**	(15)
 **9a**	Benzene,0°C, 4h rt, 3h reflux, 1h	α α/β 3:1 α/β 1:1  (95%) **9b**	
 **10a**	Benzene,0°C, 10h	 (75%) **10b**	
 **11a**	THF, rt, 2h	 **11b** (60%)	
 **12a**	Benzene, 0°C, 10h	 (75%) **12b**	
 **13a**	Benzene, rt, 8h	 (66%) **13b**	
 **14a**	Benzene, rt, 4h reflux, 1h	 (95%) **14b**	
 **15a**	Benzene, rt, 3h	 **15b** (85%)  **15c** (10%)	

diols, such as **4a**, yield a significant amount of carbonyl derivative (**4c**), along with the expected epoxide (**4b**); in the case of benzyl derivatives, such as **15a**, the carbonyl compound is favoured.

The relative stereochemistry of compounds **9a–b**, **10a–b**, **11a–b** and **14a–b** was established on the

basis of spectroscopic evidence and through NOE experiments.[18] The ^{1}H NMR spectrum of **9b** showed overlapped signals, making analysis of the NOE experiments difficult. This compound undergoes easy oxidation by air to the corresponding acid **9c**, whose spectrum was unequivocally assigned. Diols **11a**–**13a** are intermediates of our synthetic research and were chemically correlated. Compounds **12b** and **13b** showed identical properties to those reported in the literature.[16,17]

In summary, this reaction, which takes place under neutral conditions, constitutes a mild alternative for preparing carbonyl derivatives from alkenes.

Acknowledgements

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17. Simmons, D. P.; Reichlin, D.; Skuy, D. *Helv. Chim. Acta* **1988**, *71*, 1000–1006.
18. All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (s, 3H, Me-C_2), 0.99 (s, 3H, Me-C_2), 1.10 (bd, J=10.1 Hz, H-7), 1.22–1.46 (m, 3H, H-5, H-6), 1.54 (m, 1H, H-5), 1.72 (bs, 1H, H-1), 2.01 (bd, J=10.1 Hz, 1H, H-7), 2.09 (dd, J=4.7, 1.3 Hz, 1H, H-4), 2.55 (bs, 2H, OH), 3.56 (d, J=11.2 Hz, 1H, C*H*$_2$OH), 3.68 (d, J=11.2 Hz, 1H, C*H*$_2$OH). Observed NOEs: 3.56 and 3.68 with 0.90; 0.99 with 2.01. Compound **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (s, 3H, Me-C_2), 1.13 (s, 3H, Me-C_2), 1.28 (dt, J=9.9, 1.5 Hz, 1H, H-7), 1.34–1.51 (m, 2H, H-5, H-6), 1.59–1.74 (m, 3H, H-5, H-6, H-7), 1.89 (dd, J=3.2, 1.5 Hz, 1H, H-4), 2.09 (ddd, J=3.8, 2.3, 2.3 Hz, 1H, H-3), 2.53 (t, J=4.2 Hz, 1H, H-1), 9.84 (d, J=2.3 Hz, 1H, CHO). Compound **9c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 3H, Me-C_2), 1.12 (s, 3H, Me-C_2), 1.25 (bd, J=10.1 Hz, 1H, H-7), 1.33 (m, 1H, H-5), 1.41 (m, 1H, H-6), 1.63 (d, J=10.1 Hz, 1H, H-7), 1.68 (m, 1H, H-5), 1.86 (bs, 1H, H-4), 1.97 (m, 1H, H-6), 2.38 (bs, 1H, H-3), 2.44 (bs, 1H, H-1), 10.32 (s, 1H, COOH). Observed NOE: 2.38 with 1.25. Compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (s, 3H, Me-C_6), 1.20 (s, 3H, Me-C_6), 1.25 (m, 1H, H-5), 1.80–1.95 (m, 3H, H-3, H-4, H-5), 2.10 (m, 1H, H-3), 2.25 (m, 1H, H-5), 2.38 (m, 1H, H-7), 2.53 (m, 1H, H-1), 2.74 (m, 1H, H-2), 9.75 (s, 1H, CHO). Observed NOEs: 9.75 with 0.70 and 1.20. Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 3H, Me-16), 0.79 (s, 3H, Me-15), 0.86 (s, 3H, Me-14), 1.20–1.60 (m, 10H, H-2, H-2′, H-6, H-6′, H-7, H-1, H-3, H-9, H-11), 1.71 (m, 2H, H-3, H-11), 1.95 (m, 1H, H-7), 2.33 (m, 1H, H-2), 2.43 (bt, J=5.0 Hz, 1H, H-8), 3.62 (t, J=6.4 Hz, 2H, H-12), 4.48 (d, J=12.0 Hz, 1H, OCH_2Ph), 4.55 (d, J=12.0 Hz, 1H, OCH_2Ph), 7.38 (m, 5H, Bn), 10.01 (s, 1H, H-13). Observed NOE: 10.01 with 0.74. Compound **14b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3H, Me-Si), 0.04 (s, 3H, Me-Si), 0.83 (s, 3H, Me-13), 0.85 (s, 3H, Me-14), 0.87 (s, 9H, *t*-Bu-Si), 0.94 (dt, J=13.0, 3.9 Hz, 1H, H-1α), 1.04 (d, J=6.4 Hz, 3H, Me-12), 1.12 (m, 1H, H-9), 1.14 (s, 3H, Me-15), 1.17 (dd, J=13.5, 3.9 Hz, 1H, H-3α), 1.19 (d, J=3.8 Hz, H-5), 1.42 (bd, J=12.6 Hz, 1H, H-3β), 1.47 (dq, J=13.1 Hz, 1H, H-2α), 1.64 (dt, J=13.7, 10.4, 3.4 Hz, 1H, H-2β), 1.86 (bd, J=13.1 Hz, 1H, H-1β), 2.31 (d, J=13.9 Hz, 1H, H-6), 2.36 (dd, J=13.9, 3.8 Hz, 1H, H-6), 2.65 (dq, J=12.2, 6.4 Hz, 1H, H-8), 3.59 (dd, J=11.0, 4.1 Hz, 1H, H-11), 3.85 (dd, J=11.0, 1.7 Hz, 1H, H-11).