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Selective hydrolysis of *anti*-1,3-diol-acetonides for the differentiation of 1,3-*anti* and 1,3-*syn* diols

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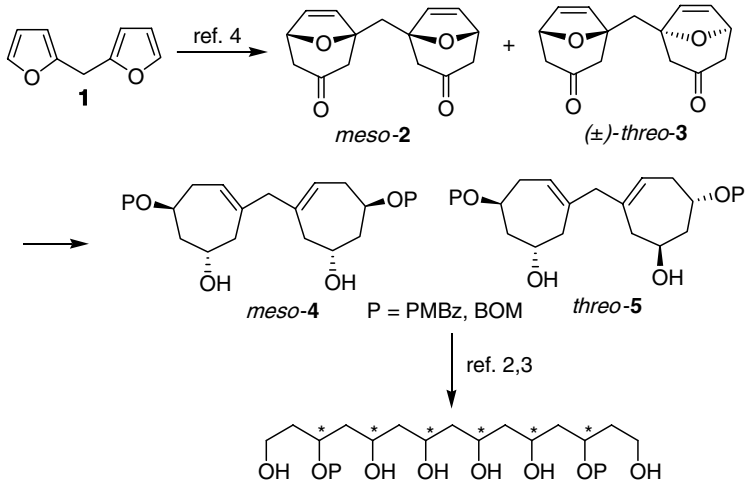
Abstract—A mild and general method for the selective cleavage of *anti*-1,3-acetonides has been developed for the differentiation of 1,3-*anti* and 1,3-*syn* diols in long chain polyolic fragments. The diluted acidic conditions applied to these systems are compatible with other common protecting groups such as silyl ethers and benzyloxymethyl ethers.

1. Introduction

A large variety of biologically active natural products includes subarrays of 1,3-diols, in particular, the family of polyene macrolide antibiotics.[1] Vogel's group has developed a non-iterative asymmetric synthesis of 15-carbon 1,3-polyols based on the stereoselective functionalization of dialkenes of type *meso*-**4**[2] and *threo*-**5**,[3] readily obtained from the bicycloadducts resulting from the double [4+3]-cycloaddition of 2,2′-methylenedifuran to 1,1,3-trichloro-2-oxyallyl cation (Scheme 1).[4] For the assignment of relative configurations[5] and for synthetic purposes, 1,3-polyols are often protected as polyacetonides. Nevertheless, it remains a difficult task to achieve selective protection of one 1,3-diol subunit in a long chain polyolic fragment. Despite the fact that differences in the rate of hydrolysis of diastereoisomeric 1,3-diol-acetonides have been reported,[6] very few applications



Scheme 1. Synthesis of long chain polyols.

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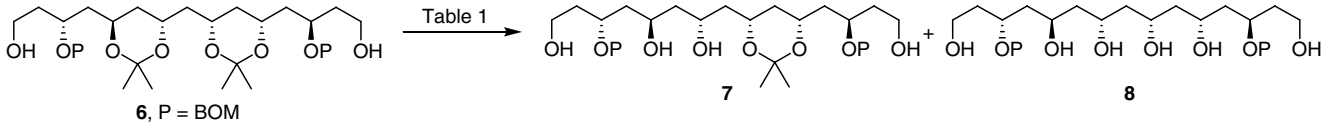
of these kinetic data have been proposed. Inspired by the work of Müller and co-workers[7] on the diastereoisomer-differentiating hydrolysis of 1,3-diol-acetonides, we have developed mild and general conditions for the selective cleavage of *anti*-1,3-diol-acetonides in the presence of *syn*-1,3-diol-acetonides on the same molecule.

2. Results and discussion

In order to explore various conditions for the selective cleavage of *anti*-1,3-diol-acetonides, the previously reported diacetonide **6**[3] was used as a model polyolic fragment (Scheme 2). We first applied the conditions reported by Müller for the selective hydrolysis of simple *anti*-diol-acetonide (Table 1, entry 1). Unfortunately, a low conversion was observed and prolonged reaction time led to the unselective deprotection of both *anti*- and *syn*-diol-acetonides. Pyridinium *p*-toluene sulfonate was then used to promote acetonide cleavage in CH_2Cl_2, but only led to the recovery of the starting polyol **6** (entries 2–3). Addition of methanol as a co-solvent afforded a moderate 40% yield of the expected monoacetonide **7**, together with the fully deprotected tetraol **8** (60%). The same lack of selectivity was obtained in the presence of camphorsulfonic acid and *p*-toluenesulfonic acid, at 0 °C, in CH_2Cl_2 (entries 5 and 7). Acidic alumina was uneffective to promote acetonide cleavage (entry 6). Finally, we found out that the use of 5 mol % of *p*-toluenesulfonic acid at −20 °C in CH_2Cl_2, afforded monoacetonide **7** in 80% yield, without concomitant undesired cleavage of the *syn*-1,3-diol acetonide (entry 8).

In order to validate the applicability of these conditions, another diacetonide derivative was prepared (Scheme 3). Ozonolysis of dialkene *meso*-**9** followed by reductive treatment with Me_2S and then with an excess of $Me_4NBH(OAc)_3$[8] afforded a mixture of hemiacetals **10**, that were not purified but subsequently reduced to the

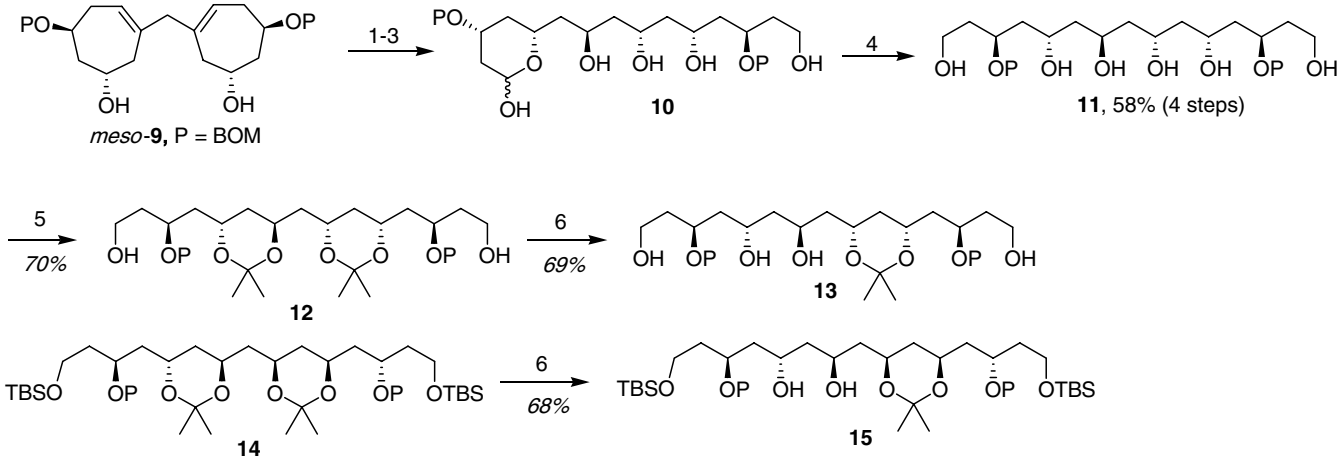


Scheme 2. Selective hydrolysis of *anti*-1,3-diol-acetonides.

Table 1.

Entry	Conditions	**7**[a] (% yield)	**8**[a] (% yield)	**6**[a] (% yield)
1	2 M HCl 0.05 equiv, CH_2Cl_2 (0.15 M), 25 °C			21
2	PPTS 0.2 equiv, CH_2Cl_2 (0.05 M), 0 °C			100
3	PPTS 0.6 equiv, CH_2Cl_2 (0.05 M), 25 °C			100
4	PPTS 0.6 equiv, CH_2Cl_2/MeOH (3:1, 0.05 M), 0 °C	40	60	—
5	CSA 0.7 equiv, CH_2Cl_2 (0.1 M), 0 °C	37	53	—
6	Acidic alumina, CH_2Cl_2 (0.1 M), 25 °C			100
7	*p*-TsOH 0.2 equiv, CH_2Cl_2 (0.05 M), 0 °C	46	29	—
8	*p*-TsOH 0.05 equiv, CH_2Cl_2 (0.05 M), −20 °C	80	—	—

[a] Isolated yield.



Scheme 3. Reagents and conditions: (1) O_3, CH_2Cl_2, −78 °C; (2) Me_2S, −78 °C; (3) $Me_4NBH(OAc)_3$, 0 °C, MeCN/AcOH; (4) $NaBH_4$, 25 °C; (5) $Me_2C(OMe)_2$/acetone, *p*-TsOH cat., 0 °C, then PPTS, CH_2Cl_2; (6) *p*-TsOH 5%, CH_2Cl_2, −20 °C.

corresponding polyol **11** in 58% yield. Treatment with $Me_2C(OMe)_2$ and acetone, in the presence of a catalytic amount of *p*-TsOH, afforded diacetonide **12**. The conditions described above were successfully applied to this derivative, resulting in the selective cleavage of the *anti*-1,3-diol-acetonide to provide monoacetonide **13** in 70% yield. In synthetic studies, silyl groups are among the most widely used protecting moieties for alcohols. For that purpose we also tested the compatibility of our conditions with *tert*-butyldimethylsilyl groups as exemplified by the selective deprotection of the 1,3-*anti* diol moiety from the silylated polyol **14**, in the presence of 5 mol % of *p*-toluenesulfonic acid, which provided monoacetonide **15** in 68% yield. No trace of deprotection of the primary alcohols was observed.

3. Conclusion

The differentiation of alcohol moieties from polyolic fragments is often required for the selective functionalization of synthetic intermediates. In this context, the mild conditions reported here represent a new alternative for the selective deprotection of *anti*-1,3-diols from polyacetonide derivatives.

3.1. General procedure for the selective hydrolysis

The polyacetonide derivative was dissolved in dichloromethane (concentration: 0.05 M) and the solution was cooled to −20 °C. *p*-Toluene sulfonic acid (0.05 equiv) was added and the mixture was stirred at −20 °C for 3 h (monitoring by TLC). The reaction mixture was directly purified by flash chromatography (4% MeOH/CH_2Cl_2) to afford the monodeprotected derivative as a colorless oil. Otherwise, the reaction mixture could also be worked-up by pouring into a satd aq solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (three times). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified as mentioned above.

Data for **7**. $[\alpha]^{23}_{405}$ −223, $[\alpha]^{23}_{435}$ −120, $[\alpha]^{23}_{577}$ −22, $[\alpha]^{23}_{589}$ −10 (*c* 0.4, MeOH). IR (film): 3415, 2940, 1650, 1430, 1380, 1265, 1200, 1160, 1100, 1035, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): $\delta = 7.38$–7.24 (m, 10H), 4.82 (s, 4H), 4.64–4.60 (m, 4H), 4.13–4.09 (m, 2H), 4.08–3.96 (m, 4H), 3.67 (t, 4H, $^3J = 6.7$), 1.82–1.77 (m, 4H), 1.69–1.65, 1.63–1.42 (2m, 10H), 1.42, 1.29 (2s, 6H) ppm. ^{13}C NMR (100 MHz, MeOD): $\delta = 138.8$, 128.4, 127.9, 127.7, 98.9, 94.5, 94.4, 73.5, 73.4, 69.8, 67.5, 66.2, 65.3, 64.4, 58.5, 44.8, 44.4, 43.7, 43.1, 38.4, 38.3, 37.6, 29.6, 19.2 ppm. MALDI-MS: 643.46 (M+Na), 659.45 (M+K). $C_{34}H_{52}O_{10}$ (620.775): calcd C 65.78, H 8.44; found C 65.75, H 8.49.

Data for **12**. IR (film): 3445, 3065, 3030, 2990, 2940, 1495, 1455, 1380, 1225, 1165, 1025, 940, 810, 740, 700 cm^{-1}. ^1H NMR (C_6D_6, 400 MHz, 25 °C): $\delta = 7.33$–7.06 (m, 10H), 4.77–4.70 (m, 4H), 4.62, 4.50 (2d, 2H, $^2J = 12.0$), 4.61, 4.47 (2d, 2H, $^2J = 12.0$), 4.21–3.86 (m, 6H), 3.74, 3.64 (2m, 4H), 2.05–1.98 (m, 4H), 1.78–1.31 (m, 10H), 1.40, 1.38, 1.33, 1.27 (4s, 12H) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz, 25 °C): $\delta = 139.1$, 129.3, 129.2, 128.5, 101.1, 99.3, 95.6, 95.5, 75.3, 74.3, 70.4, 66.6, 65.9, 64.5, 63.0, 60.0, 43.7, 43.4, 43.1, 40.1, 39.3, 39.2, 31.2, 25.8, 25.7, 20.6 ppm. CI-MS (NH_3): 678 (1, $[M+NH_4^+]$), 645 (2), 91 (100). $C_{37}H_{56}O_{10}$ (660.839): calcd C 67.25, H 8.54; found C 67.25, H 8.79.

Data for **13**. IR (film): 3415, 2945, 1650, 1430, 1285, 1200, 1160, 1100, 1035, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): $\delta = 7.38$–7.15 (m, 10H), 4.83–4.78 (s, 4H), 4.67–4.60 (m, 4H), 4.12–3.95 (m, 6H), 3.70–3.65 (m, 4H), 1.82–1.75 (m, 4H), 1.62–1.29 (2m, 10H), 1.39, 1.30 (2s, 6H) ppm. ^{13}C NMR (100 MHz, MeOD): $\delta = 138.3$, 128.4, 128, 127.7, 99.0, 94.6, 94.5, 73.4, 72.8, 69.8, 69.7, 66.3, 66.0, 65.1, 64.6, 58.5, 58.4, 45.8, 44.7, 43.7, 42.9, 38.5, 38.3, 38.1, 29.6, 19.3 ppm. MALDI-MS: 643.31 (M+Na), 659.28 (M+K). $C_{34}H_{52}O_{10}$ (620.775): calcd C 65.78, H 8.44; found C 65.72, H 8.35.

Data for **15**. IR (film): 3520, 2940, 2860, 1733, 1465, 1380, 1255, 1200, 1165, 1105, 1040, 840, 780, 740, 700, 660 cm^{-1}. ^1H NMR (400 MHz, MeOD): $\delta = 7.50$–7.24 (m, 10H), 4.83 (s, 4H), 4.26, 4.63 (2s, 4H), 4.20–3.85 (2m, 6H), 3.74 (t, 4H, $^3J = 5.7$), 1.78–1.40 (m, 4H), 1.78–1.40 (2m, 10H), 1.42, 1.28 (2s, 6H), 0.92 (s, 18H), 0.13 (s, 12H) ppm. ^{13}C NMR (100 MHz, MeOD): $\delta = 138.3$, 128.4, 127.9, 127.7, 98.9, 94.6, 94.5, 73.5, 69.8, 67.5, 66.2, 65.3, 64.4, 59.7, 44.7, 44.4, 43.8, 43.3, 38.8, 37.6, 29.6, 19.3, 25.4, 24.1, −6.2 ppm. MALDI-MS: 871.61 (M+Na), 887.58 (M+K). $C_{46}H_{80}O_{10}Si_2$ (849.292): calcd C 65.05, H 9.49, Si 6.61; found C 65.75, H 9.55, Si 6.54.

Acknowledgements

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