Pergamon

Tetrahedron Letters 43 (2002) 7477–7479

TETRAHEDRON LETTERS

Synthesis of protected *syn* 1,3-diols by intramolecular conjugate addition to vinyl sulfones

Laurence Grimaud, Delphine Rotulo, Rafael Ros-Perez, Ludivine Guitry-Azam and Joëlle Prunet*

Laboratoire de Synthèse Organique associé au CNRS, UMR 7652, DCSO, Ecole Polytechnique, 91128 Palaiseau, France

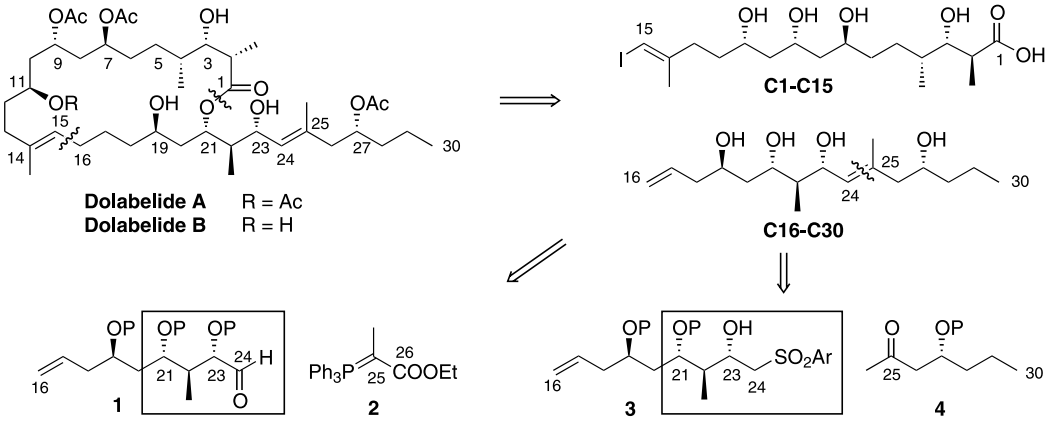
Received 6 August 2002; accepted 27 August 2002

Abstract—A short route to sulfones **9a–c** is described. These synthons encompassing a *syn* 1,3-diol motif are model compounds for the C16–C24 fragment of Dolabelides. The benzylidene protecting group can be reduced regioselectively to furnish β-hydroxysulfones **10a–b**. First attempts of Julia coupling of the dianions derived from these substrates with aldehydes and ketones are also reported.

Dolabelides A and B, two 22-membered ring lactones, were isolated in 1995 from the sea hare *Dolabella auricularia* (family Aplysiidae) by Yamada and co-workers (Scheme 1).[1] Two similar 24-membered ring lactones, Dolabelides C and D, were also extracted from the same source in 1997.[2] These compounds exhibit cytotoxicity against $HeLaSe_3$ cell lines with IC_{50} values of 6.3, 1.3, 1.9 and 1.5 μg/mL, respectively. Their structures were determined by HRFAB mass spectroscopy and 2D NMR, and their absolute configuration by the modified Mosher method.[3]

The planned retrosynthesis is shown in Scheme 1. Opening of the macrolactone, followed by C15–C16 disconnection furnishes two fragments of roughly equal size, C1–C15 and C16–C30. They would be assembled by a Suzuki coupling[4] between a vinyl iodide at C15 and a borane derived from the olefin at C16. The C16–C30 portion can be further disconnected through the C24–C25 double bond. In a previous paper,[5] we described the synthesis of the required C16–C24 aldehyde **1** for a Wittig reaction with phosphorane **2**. An alternative to make the C24–C25 bond would be a Julia coupling between sulfone **3** and ketone **4**.

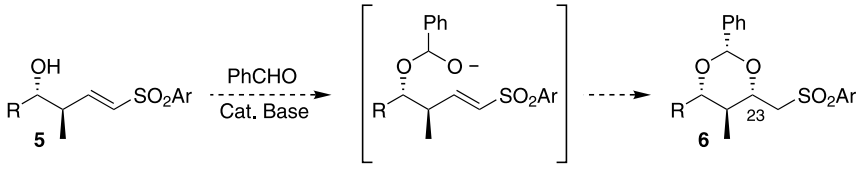
We wish to report here a new method for the diastereoselective construction of such sulfones, encompassing a 1,3-diol motif at the 2 and 4 positions.



Scheme 1.

* Corresponding author. E-mail: joelle.prunet@polytechnique.fr

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01796-3



Scheme 2.

We wanted to install the hydroxyl group at C23 by an intramolecular conjugate addition of a hemiacetal anion, made in situ from an homoallylic alcohol in the presence of benzaldehyde and a catalytic amount of base, which would lead to compound **6** (Scheme 2). A conjugate addition of this type has been reported by Evans and Prunet,[6] where the double bond of the starting substrate is conjugated to an ester or a Weinreb amide. Here the Michael acceptor would be a vinyl sulfone.

In order to test the feasibility of this new reaction, we synthesized several model homoallylic alcohols as shown in Scheme 3. Alcohols **7a–c** were treated with freshly prepared *p*-toluenesulfonyl iodide[7] according to Edwards' method[8] with a slight modification: the subsequent elimination step was effected in THF at room temperature instead of THF/toluene at −78°C. This method does not require the protection of the homoallylic alcohol function, and furnishes the *E* isomer exclusively in excellent yields.

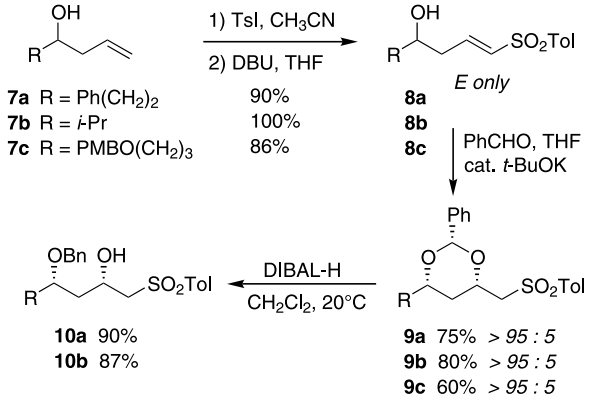
The intramolecular conjugate addition in the presence of benzaldehyde and a catalytic amount of potassium *tert*-butoxide proceeded in good yields and selectivity. Moreover, if the intermediate sulfones **8a–b** were not purified, the protected *syn* 1,3-diols **9a–b** were obtained from **7a–b** in 60 and 82% yield, respectively, for the three steps. The major diastereomer is the thermodynamically favored product, where all the substituents are equatorial on the dioxane ring.† Sulfones **9a–c** were prone to β-elimination under the basic conditions required for the Julia coupling. To circumvent this problem, the benzylidene acetal in **9a** and **9b** was reduced with DIBAL-H to furnish monoprotected diols **10a** and **10b** in excellent yields. The reduction was totally regioselective, in accordance to the reduction of benzylidene acetals flanked with a benzyl-protected alcohol,[9] and generated a free alcohol next to the sulfone group. To our knowledge, this is the first case of a benzylidene acetal reduction directed by a sulfone group.

Addition of dianions of β-hydroxysulfones to aldehydes[10] and ketones[11] have been reported. When using the literature conditions, condensation of the dianion of **10a** or **10b** with dihydrocinnamaldehyde, isobutyraldehyde, benzaldehyde or acetone led to the desired adducts in modest yields with diastereoselectivities ranging from 2:1 to 6:1 (Scheme 4). The configuration of the major diastereomers was proved by ^{1}H and ^{13}C NMR analysis of the derived acetonides.[10a] The conversion is low, but in all cases most of the starting sulfone can be recovered. We are currently screening diverse bases to improve both the yield and the selectivity of this reaction.

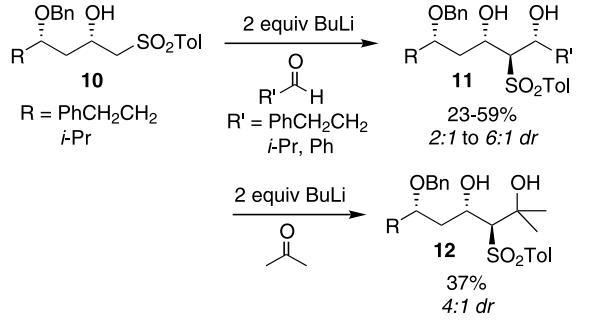
In summary, we have developed a new method to make sulfone synthons with a *syn* 1,3-diol motif. These compounds constitute models for the C16–C24 portion of Dolabelides. Julia coupling reactions of the dianions of these β-hydroxysulfones with aldehydes and ketones were attempted, and optimization of this coupling is in progress.

Experimental procedures for 8b, 9b and 10b

To a solution of 400 mg (3.5 mmol) of homoallylic alcohol **7b** in 5 mL of acetonitrile at room temperature was added a solution of 1.1 g (3.9 mmol, 1.1 equiv.) of freshly prepared tosyl iodide in 7 mL of acetonitrile (rinse 2×5 mL). The resulting solution was stirred for 1 h 30 min at 20°C to give, after evaporation of the solvent, the β-iodosulfone. The crude product was



Scheme 3.



Scheme 4.

† The relative configuration of the three stereogenic centers was proved by NOE effects.

treated with a solution of 630 μL of DBU (3.9 mmol, 1.1 equiv.) in 10 mL of THF at 20°C. The resulting solution was stirred for 45 min at 20°C and quenched with 20 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3×20 mL of Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give without further purification 941 mg (100%) of the substituted (*E*)-vinylsulfone **8b** as a brown oil: **^{1}H NMR** (200 MHz, $CDCl_3$) δ 7.81–7.73 (m, 2H), 7.33–7.22 (m, 2H), 7.02 (dt, $J=15.0$, 7.2 Hz, 1H), 6.41 (dt, $J=15.0$, 1.4 Hz, 1H), 3.55–3.35 (m, 1H), 2.40 (s, 3H), 2.40–2.20 (m, 2H), 1.74–1.58 (m, 1H), 0.92, 0.91 (2d, $J=6.8$ Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 144.1, 143.6, 137.7, 132.6, 129.8, 127.6, 74.7, 36.2, 33.6, 21.5, 18.5, 17.2; **IR** (thin film) 3519, 3047, 2960, 2874, 1666, 1633, 1597, 1495, 1469, 1316, 1144 cm^{-1}; **Anal**. calcd for $C_{14}H_{20}O_3S$: C, 62.65; H, 6.51. Found: C, 62.71; H, 7.62.

To a solution of 240 mg (0.90 mmol) of vinylsulfone **8b** in 5 mL of THF at 0°C was added 105 μL (1.0 mmol, 1.1 equiv.) of freshly distilled benzaldehyde, followed by 10 mg (0.1 mmol, 0.1 equiv.) of *t*-BuOK, and the resulting solution was stirred for 15 min at 0°C. This sequence (addition/stirring) was repeated twice, and the reaction mixture was quenched with 30 mL of saturated aqueous NH_4Cl. The aqueous phase was extracted with 3×30 mL of Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Analysis of the ^{1}H NMR of the unpurified product showed a >95:5 ratio of diastereomers. The resulting yellow solid was recrystallized from ethyl acetate/petroleum ether (1:3) to give 267 mg (80%) of **9b** as a cotton-like white solid: **mp** 139–140°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2H), 7.28–7.10 (m, 7H), 5.41 (s, 1H), 4.50–4.37 (m, 1H), 3.63–3.48 (m, 1H), 3.57 (dd, $J=14.6$, 7.6 Hz, 1H), 3.26 (dd, $J=14.6$, 3.9 Hz, 1H), 2.41 (s, 3H), 1.84–1.70 (m, 2H), 1.48 (q, $J=11.3$ Hz, 1H), 0.99, 0.93 (2d, $J=6.8$ Hz, 6H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 144.5, 138.0, 137.5, 129.7, 128.5, 128.1, 127.8, 125.9, 100.3, 81.4, 71.6, 61.8, 33.4, 32.8, 21.5, 18.1, 17.8; **IR** (KBr) 3032, 2993, 1639, 1451, 1401, 1300, 1143, 1106, 1086, 1026 cm^{-1}; **MS** (GC, CI NH_3) *m*/*z* 375 (M+H$^+$), 269; **Anal**. calcd for $C_{21}H_{26}O_4S$: C, 67.35; H, 7.00. Found: C, 67.19; H, 7.11.

To a solution of 660 mg (1.8 mmol) of benzylidene acetal **9b** in 7 mL of CH_2Cl_2 at 0°C was added 12 mL (5.5 mmol, 10 equiv.) of a solution of DIBAL-H (1.5 M in toluene). The resulting solution was stirred for 45 min at 20°C. To the solution was added dropwise 4 mL of EtOAc to neutralize the excess of DIBAL-H, and the reaction mixture was quenched with 30 mL of saturated aqueous potassium–sodium tartrate solution and diluted with 30 mL of Et_2O. The resulting two-phase mixture was stirred for 1.5 h at 20°C, and the layers were separated. The aqueous phase was extracted with 3×40 mL of Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography on silica gel (ether/petroleum ether 60:40) to give 576 mg (87%) of **10b** as white crystals: **mp** 43–44°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, $J=8.2$ Hz, 2H), 7.35–7.25 (m, 7H), 4.58 (d, $J=11.2$ Hz, 1H), 4.37–4.32 (m, 1H), 4.35 (d, $J=11.2$ Hz, 1H), 3.95 (s, 1H), 3.52–3.48 (m, 1H), 3.30 (dd, $J=14.3$, 7.7 Hz, 1H), 3.20 (dd, $J=14.3$, 3.8 Hz, 1H), 2.44 (s, 3H), 2.11–2.06 (m, 1H), 1.75–1.65 (m, 2H), 0.90, 0.88 (2d, $J=6.6$ Hz, $J=6.8$ Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.7, 137.9, 136.8, 129.8, 128.3, 127.9, 127.6, 82.4, 71.0, 65.5, 62.5, 35.6, 29.4, 21.5, 18.2, 16.3; **IR** (KBr) 3503 (br), 3030, 2960, 2872, 1598, 1496, 1454, 1388, 1301, 1139, 1087, 1068, 1028 cm^{-1}; **MS** (GC, CI NH_3) *m*/*z* 394 (M+NH_4^+), 377 (M+H$^+$), 359, 269, 188; **Anal**. calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.95; H, 7.59.

Acknowledgements

The CNRS and the Ecole Polytechnique are thanked for financial support.

References

1. Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett*. **1995**, *36*, 7491.
2. Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod*. **1997**, *60*, 155.
3. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.
4. For a recent use of such a coupling reaction, see: Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 209 and references cited therein.
5. Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett*. **2002**, *4*, 419.
6. Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem*. **1993**, *58*, 2446.
7. Edwards, G. L.; Muldoon, C. A.; Sinclair, D. J. *Tetrahedron* **1996**, *52*, 7779.
8. Craig, D. C.; Edwards, G. L.; Muldoon, C. A. *Synlett* **1997**, 1318.
9. Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett*. **1983**, 1593.
10. (a) Tanikaga, R.; Hosoya, K.; Kaji, A. *Chem. Lett*. **1987**, 829; (b) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2397.
11. Kim, K. S.; Sohng, J.-K.; Ha, S. B. *Tetrahedron Lett*. **1988**, *29*, 2847.