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Tandem Conjugate Addition–Elimination for the Diastereoselective Synthesis of 4*E*-Alkenyl *syn*-1,3-Diols

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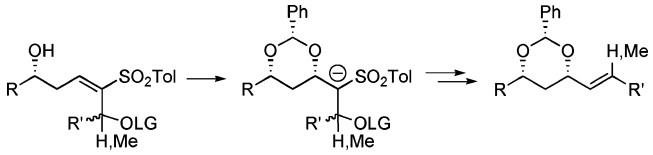
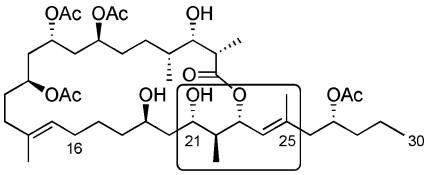
ABSTRACT



We have developed a tandem conjugate addition–elimination sequence for the diastereoselective synthesis of protected allylic *syn*-1,3-diols, starting from vinyl sulfones. The sulfonyl group was then reduced with sodium amalgam to furnish the *E*-olefin as the major isomer. This method was applied to the synthesis of a trisubstituted alkene modeling the C21–C25 fragment of Dolabelide C.

Dolabelide C (Figure 1) is a member of a family of four macrolactones (Dolabelides A−D) isolated from the sea hare



Dolabelide C

Figure 1.

Dolabella auricularia (family Aplysiidae).[1] It has been shown to exhibit cytotoxic activity against HeLa−S_3 cell lines with an IC_{50} of 1.9 μg/mL. We[2] and others[3] have described syntheses of Dolabelide fragments, and the total synthesis of Dolabelide D has recently been reported by Leighton and co-workers.[4]

The C21−C25 portion of this molecule encompasses a *syn*-1,3-diol motif flanked by a trisubstituted olefin (Figure 1). We envisaged to install these functional groups by a stereoselective intramolecular conjugate addition of a hemiacetal anion formed in situ from a δ-hydroxy vinyl sulfone and benzaldehyde in the presence of base, followed by elimination of a suitable leaving group (Scheme 1). The resulting vinyl sulfone would then be reduced to the corresponding olefin. Such a conjugate addition on simple vinyl sulfones like **1a**−**c** (eq 1) has already been reported by us.[5]

We first embarked on the synthesis of model substrates of the C21−25 fragment lacking the methyl groups at C22

(1) Isolation of Dolabelides A and B: Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491. Isolation of Dolabelides C and D: Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155.

(2) C16−C24: Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419. C1−C15: Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47*, 4075−4077.

(3) (a) C15−C24 and C25−C30: Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Bonini, C.; Genêt, J.-P. *Tetrahedron Lett.* **2003**, *44*, 1763. C1−C13: Le Roux, R.; Desroy, N.; Phansavath, P.; Genêt, J.-P. *Synlett* **2005**, 429. (b) C15−C30: Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535. (c) C1−C13: Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911.

(4) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796.

(5) Grimaud, L.; Rotulo, D.; Ros-Perez, R.; Guitry-Azam, L.; Prunet, J. *Tetrahedron Lett.* **2002**, *43*, 7477.

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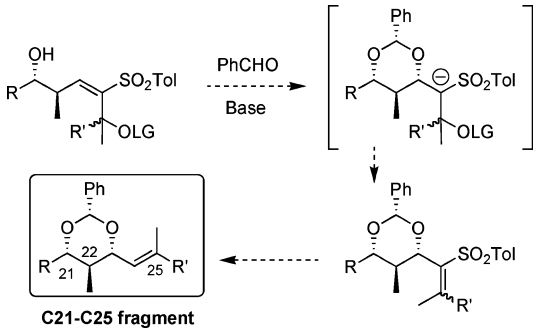
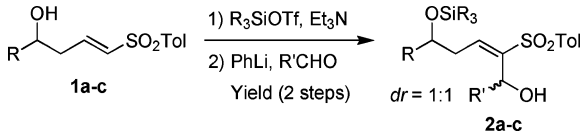
Scheme 1



and C25, starting with compounds **1a**−**c**.[5] After conversion of the hydroxyl group into the corresponding triethyl or *tert*-butyldimethylsilyl ethers using the appropriate triflate reagent,[6] these vinyl sulfones were deprotonated with phenyllithium[7] and condensed with isobutyraldehyde or propionaldehyde to furnish *E*-olefins **2a**−**c** as 1:1 inseparable mixtures of diastereomers in good overall yields (Table 1).

Table 1.

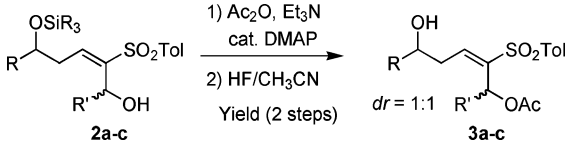


R	precursor	SiR_3	R′	product	yield
$PhCH_2CH_2$	**1a**	TBS	*i*-Pr	**2a**	65%
Ph	**1b**	TES	Et	**2b**	56%
n-Bu	**1c**	TES	*i*-Pr	**2c**	78%

The lower yield observed in the case of **2b** is due to competitive elimination of the benzylic OTES group during the condensation reaction.

Hydroxy adducts **2a**−**c** were then acetylated,[8] and the silyl ethers were subsequently hydrolyzed with HF in acetonitrile to give the required substrates **3a**−**c** for the conjugate addition of (Table 2).[9]

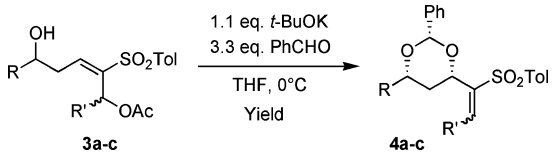
Table 2.



R	SiR_3	R′	precursor	product	yield
$PhCH_2CH_2$	TBS	*i*-Pr	**2a**	**3a**	80%
Ph	TES	Et	**2b**	**3b**	66%
n-Bu	TES	*i*-Pr	**2c**	**3c**	81%

Treatment of homoallylic alcohols **3a**−**c** with excess benzaldehyde and potassium *tert*-butoxide led to the expected

Table 3.



R	R′	precursor	product	yield	*syn*/*anti*	*E*/*Z*
$PhCH_2CH_2$	*i*-Pr	**3a**	**4a**	83%	94:6	1:1
Ph	Et	**3b**	**4b**	57%	91:9	3.5:1
n-Bu	*i*-Pr	**3c**	**4c**	80%	93:7	1.3:1

benzylidene acetals **4a**−**c** with excellent *syn*/*anti* selectivity (>90:10) (Table 3). The *E*/*Z* ratios range from 1:1 (R = $PhCH_2CH_2$, *n*-Bu) to 3.5:1 (R = Ph). During the optimization of the reaction conditions, we observed that higher *E*/*Z* ratios were obtained when the yields were lower. For example, when the base was added portionwise (0.3 equiv every 15 min), benzylidene acetal **4a** was obtained in 65% yield with a 3:1 *E*/*Z* ratio. We supposed that the reaction is stereospecific and that the diastereomer leading to the *Z* product (or the *Z* product itself) decomposes more readily than the one furnishing the *E* olefin (or the *E* olefin itself). Unfortunately, we could not prove this hypothesis because the diastereomers are inseparable at all stages. Compound **3b** (R = Ph) is more sensitive to basic conditions than the other vinyl sulfones, as was the case for **1b** and **2b**, and some decomposition occurs even under optimized reaction conditions, leading to an increased *E*/*Z* ratio (3.5:1).

The stereochemistry of the major isomers of compound **4c** was proven by NOE experiments (Figure 2).

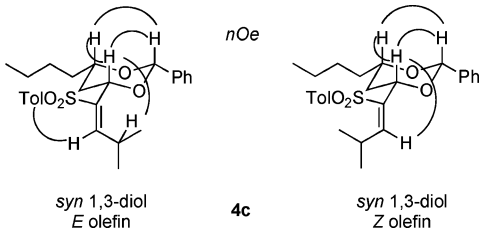


Figure 2. NOE observed with the *ortho* proton in the Tol group.

The conjugate addition on simple vinyl sulfones such as **1a**−**c** is under thermodynamic control,[5,10] leading to the all-*cis* benzylidene acetal corresponding to the protected *syn*-

(6) Use of the silyl chloride reagents with imidazole for 60 h (the reaction was very slow) led to formation of 5−10% of the allylic sulfones resulting from olefin isomerization.

(7) Rotulo-Sims, D.; Grimaud, L.; Prunet, J. *CR Chimie* **2004**, 941.

(8) No isomerization to the allylic sulfones was observed in the presence of triethylamine, probably because of the short reaction times (30 min to 3 h).

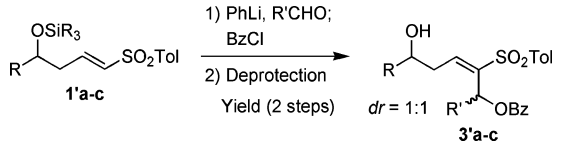
(9) Acetylation of **2b** proceeds in lower yield because of its base sensitivity.

(10) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446−2453.

diol. The excellent *syn* selectivity obtained in the case of compounds **4a**−**c** proves that the thermodynamic equilibrium of the conjugate addition is reached before the elimination takes place.

To examine the influence of the leaving group on the tandem conjugate addition−elimination process, we then tried to synthesize the mesylate or the carbonate derivatives of alcohols **2a**−**c**. Unfortunately, the mesylate products were too unstable to be isolated, and the carbonate esters could not be formed. Formation of the corresponding benzoates was plagued by moderate conversion and partial isomerization to the allylic sulfones. However, these benzoates could be obtained by trapping in situ with 5 equiv of benzoyl chloride, the alkoxides resulting from the condensation of the δ-silyloxy vinyl sulfones **1′a**−**c** with isobutyraldehyde or propionaldehyde (Table 4). After deprotection of the silyl

Table 4.



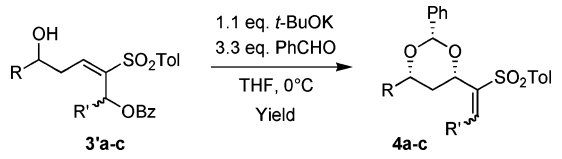
R	SiR_3	precursor	R′	product	yield
$PhCH_2CH_2$	TBS	**1′a**	*i*-Pr	**3′a**	28%[a]
Ph	TES	**1′b**	Et	**3′b**	47%[b]
C_4H_9	TES	**1′c**	*i*-Pr	**3′c**	58%[c]

[a] Along with 15% of the corresponding diol. [b] Along with 11% of the corresponding diol. [c] Along with 16% of the corresponding diol.

ethers, the resulting δ-hydroxy benzoates **3′a**−**c** were obtained in fair yields, along with a small amount of the corresponding diols.

Compounds **3′a**−**c** underwent the tandem process to produce compounds **4a**−**c** in yields and selectivities similar to the ones obtained from acetates **3a**−**c** (Table 5). The main

Table 5.

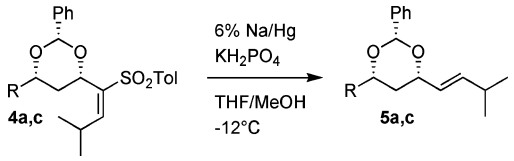


R	R′	precursor	product	yield	*syn*/*anti*	*E*/*Z*
$PhCH_2CH_2$	*i*-Pr	**3′a**	**4a**	89%	92:8	1.1:1
Ph	Et	**3′b**	**4b**	48%	93:7	3:1
C_4H_9	*i*-Pr	**3′c**	**4c**	82%	89:11	1:1

advantage of the benzoate leaving group is its in situ installation after the condensation reaction. This in situ benzoylation is crucial for the activation of tertiary alcohols (as we will see later for the synthesis of trisubstituted olefins).[11]

The next step was the reductive desulfonylation. Several methods were attempted without success. Treatment of compound **4a** with sodium dithionite mainly led to the reduction of the olefin (55%), and only 5% of the desired product **5a** was observed.[12] Use of butylmagnesium chloride in the presence of $Pd(acac)_2$ only caused degradation of sulfone **4a**.[13] However, when this compound (enriched in the *E* isomer by careful chromatography) was reduced with sodium amalgam, the desired olefin **5a** was produced in 67% unoptimized yield (Table 6).[14] In the same manner, sulfone

Table 6.

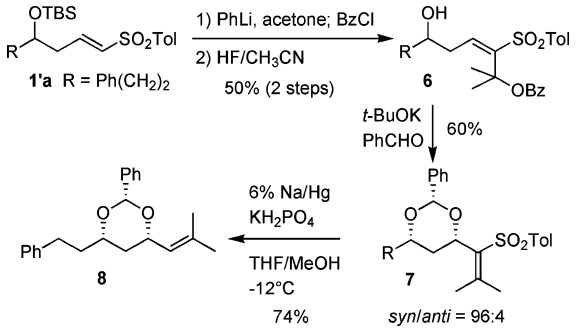


R	precursor	*E*/*Z*	product	yield	*E*/*Z*
$PhCH_2CH_2$	**4a**	3:1	**5a**	67%	93:7
n-Bu	**4c**	4:1	**5c**	55%	92:8

4c furnished alkene **5c** in 55% yield. This reduction is stereoconvergent: both isomers of the starting vinyl sulfones mainly give the *E* isomer of alkenes **5a**,**c**.[15]

Finally, to model more closely the 24,25-alkene of Dolabelide C, we applied the whole reaction sequence to the synthesis of a trisubstituted olefin. Vinyl sulfone **1′a** was condensed with acetone, and the resulting adduct was trapped in situ by benzoyl chloride (Scheme 2).[11] Deprotection of

Scheme 2



the TBS ether then furnished alcohol **6** in good overall yield. The tandem conjugate addition−elimination proceeded in excellent *syn*/*anti* selectivity. Vinyl sulfone **7** was reduced with sodium amalgam to produce trisubstituted alkene **8** in 74% yield.

(11) Two-step formation of tertiary acetates or in situ acetylation of tertiary alkoxides was not possible.

(12) Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett.* **1982**, *23*, 3265−3266.

(13) Fabre, J.-L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311−4314.

(14) Chen, S.-H.; Horvath, R. F.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834−5845.

In conclusion, we have developed an efficient and stereoselective method for the synthesis of α-unsaturated 1,3-diols. The *syn*-diol moieties are obtained with selectivities greater than 90:10, and the olefins are produced as the *E* isomers almost exclusively (≥92:8). Further studies are underway to delineate the scope of this new sequence and apply it to the synthesis of the C16−C30 portion of Dolabelide C.

(15) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194−3204. Use of SmI_2 should also reduce the vinyl sulfones but in our case did not give any of the expected products **5a**,**c**.

Acknowledgment. Financial support was provided by the CNRS and the Ecole Polytechnique. D.R.-S. acknowledges the MENR for a fellowship. We thank Dr. Laurence Grimaud for helpful discussions.

Supporting Information Available: Experimental procedures and full characterization for compounds **1′a**−**c**, **2a**−**c**, **3a**−**c**, **3′a**−**c**, **4a**−**c**, **5a**,**c**, and **6**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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