Natural Product Synthesis

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Total Synthesis and Determination of the Absolute Configuration of (−)-Dolabriferol**

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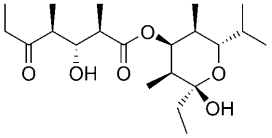
In 1996 Ciavatta et al.[1] isolated (−)-dolabriferol ((−)-**1**; Scheme 1) from *Dolabrifera dolabrifera*, a gastropod mollusk scarcely protected by a shell and collected off Cuba. The structure and relative configuration of (−)-**1** was established

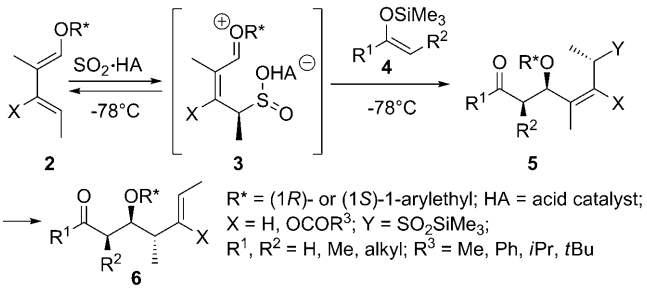


Scheme 1. (−)-Dolabriferol ((−)-**1**).

by advanced NMR studies and by single-crystal X-ray analysis, but the absolute configuration was not assigned.[1] It is assumed that (−)-**1** protects the shell-less mollusk from predators. The natural product is made of two polypropionate subunits linked by an ester function structural motif which is also found in natural products such as baconipyrones A–D[2] and siserrone A.[3] Up to now four reports have described the attempted synthesis of (−)-**1**.[4–7]

Using our reaction cascade (oxyallylation of alkenes), which combines electron-rich dienes **2** and (*Z*)-enoxysilanes **4** through SO_2 umpolung,[8,9] we have developed a one-pot synthesis of α,β,γ-*syn*,*anti*-stereotriads of type **6** (Scheme 2). The starting dienes **2** are obtained readily from pent-3-one, ethyl formate, and inexpensive enantiomerically enriched 1-arylethanol as the source of chirality.[10] The latter is transferred to the intermediate silyl sulfinates **5**, which are converted in situ into **6** in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 with high stereoselectivity (Scheme 2).[11,12]

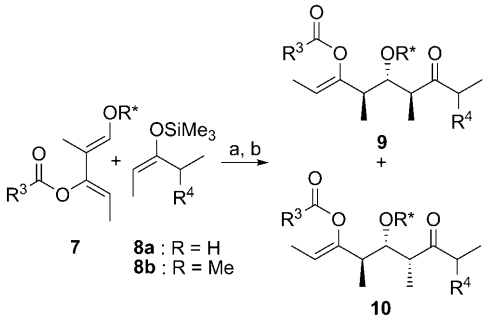
We now have found that the same reaction cascade applied to (*E*)-enoxysilanes generates the corresponding



Scheme 2. One-pot synthesis of α,β,γ-*syn*,*anti*-stereotriads through SO_2-induced oxyallylation of (*Z*)-enoxysilanes.

α,β,γ-*anti*,*anti*-stereotriads in a one-pot operation (Scheme 3, Table 1). This allowed us to develop efficient syntheses of the polypropionate subunits of (−)-**1**. We have found also a route to combine them and to construct (−)-**1**, thus realizing the first total synthesis of this natural product. We also established its absolute configuration.

The reaction of diene (+)-**7a** and silyl enol ether **8a** with an excess of SO_2/toluene in the presence of $(CF_3SO_2)_2NH$ (Tf_2NH, 20 mol%) provided a mixture of silyl sulfinates,



Scheme 3. One-pot synthesis of α,β,γ-*anti*,*anti*-stereotriads through SO_2-induced oxyallylation of (*E*)-enoxysilanes. Reagents and conditions: a) SO_2, Tf_2NH, CH_2Cl_2, −78 °C; b) $Pd(OAc)_2$ (cat.), PPh_3 (cat.), *i*PrOH, MeCN, K_2CO_3. Tf = trifluoromethanesulfonyl.

Table 1: Results of SO_2-induced oxyallylation cascade with (*E*)-enoxysilanes.

Diene	R* 1-(PhCHMe)	R^3	R^4	Yield (**9**+**10**)	Ratio **9**/**10**
(+)-**7a**	1*R*	*i*Pr	H	71%	**9aa**/**10aa** = 3:1
(+)-**7b**	1*R*	*t*Bu	H	76%	**9ba**/**10ba** = 5:1
(−)-**7c**	1*S*	Ph	Me	67%	**9cb**/**10cb** > 95:5
(−)-**7d**	1*S*	Me	Me	72%	**9db**/**10db** = 9:1

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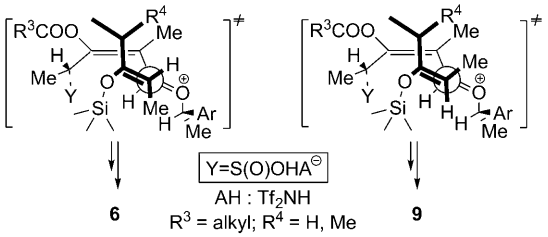
which were desulfinylated by *i*PrOH/MeCN/K_2CO_3 in the presence of $Pd(OAc)_2/PPh_3$ (10 mol%). The resulting 3:1 mixture of stereotriads **9aa** and **10aa** (71% yield) was separated readily by flash chromatography on silica gel (Scheme 3, Table 1). The reaction of (+)-**7b** and **8a** gave a 5:1 mixture of pivalates **9ba**/**10ba** in 76% yield. Single-crystal X-ray diffraction of **10ba** established its structure unambiguously. The reaction of diene (−)-**7c** with **8b** resulted in the stereotriad **9cb** which was isolated as a single diastereomer in 67% yield. The combination of (−)-**7d** and **8b** led to a readily separable 9:1 mixture of **9db** and **10db** in 72% yield.

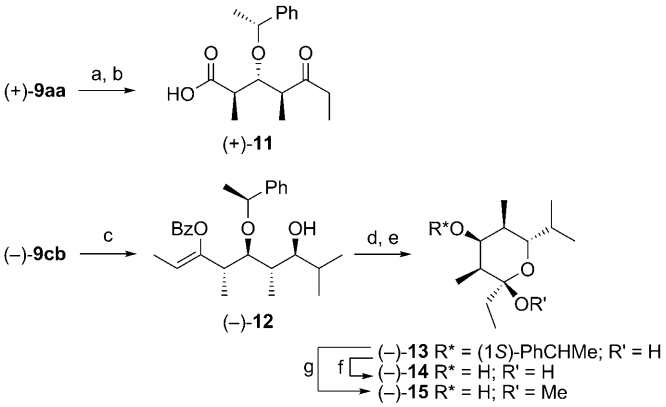
The diastereoselectivities observed for the reaction cascades in Schemes 2 and 3 are consistent with the preferred transition states shown in Scheme 4. The hetero-Diels–Alder addition of Lewis acid activated SO_2 to the least hindered face of the diene results in the formation of a zwitterionic species, which is quenched by the nucleophilic attack of the silyl enol ether to give the corresponding silyl sulfinate (e.g. **5**), which leads preferentially to stereotriads **6** starting with (*Z*)-silyl enol ethers **4**, and to diastereomers **9** starting with (*E*)-silyl enol ethers **8** after palladium-catalyzed desilylation and desulfinylation.



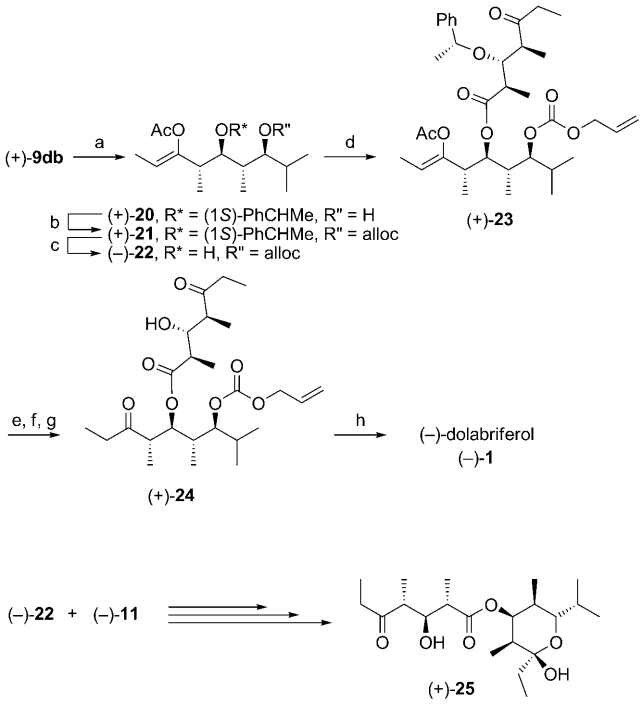
Scheme 4. Hypothetical transition structures for the oxyallylation reaction.

Ozonolysis of pure (+)-**9aa** gave the carboxylic subunit (+)-**11** of (−)-**1** in 61% yield. Reduction of ketone (−)-**9cb** with $NaBH_4$, L-selectride, $LiBH_4$, or DIBAL-H was not highly diastereoselective. Fortunately, the Evans' method[13] using Bu_3SnH and Me_3AlCl gave the pure alcohol (−)-**12** (90% yield), which was converted into (−)-**13** (91% yield). Hydrogenolysis of the phenethyl ether ($H_2/Pd(OH)_2$ in EtOAc) produced the hemiacetal subunit (−)-**14** (72% yield) (Scheme 5). Its structure was established by ^1H and ^{13}C NMR analysis and confirmed by single-crystal X-ray diffraction. The corresponding methyl acetal (−)-**15** was obtained in 69% yield by carrying out the hydrogenolysis in MeOH.

As already reported,[14] the direct esterification of analogues of (+)-**11** and (−)-**14** failed.[15,16] In order to reduce possible steric interference between these compounds, we envisioned the esterification of a suitably protected acyclic precursor of the hemiacetal (−)-**14** (Scheme 6). The enol acetate (+)-**9db** was reduced to (+)-**20** (89% yield). Protection as the allyl carbonate (+)-**21** (91% yield) followed by treatment with $TiCl_4/CH_2Cl_2$ provided (−)-**22** (69% yield). Esterification between (−)-**22** and (+)-**11** using Paterson's protocol[17] gave a 9:1 mixture of the desired diastereoisomers



Scheme 5. Conversion of stereotriads into semiprotected subunits of (−)-dolabriferol. Reagents and conditions: a) O_3, CH_2Cl_2, −78°C; b) Me_2S, H_2O, RT, 61% (over two steps); c) Me_2AlCl, Bu_3SnH, CH_2Cl_2, −78°C, 90%; d) MeLi·LiBr, DME/Et_2O, −78°C; e) H_2O/NH_4Cl, RT, 91% (over two steps); f) $Pd(OH)_2$, AcOEt, RT, 72%; g) $Pd(OH)_2$, MeOH, RT, 69%. Bz = benzoyl.



Scheme 6. Synthesis of (−)-dolabriferol and stereomer (+)-**25**. Reagents and conditions: a) Me_2AlCl, Bu_3SnH, CH_2Cl_2, −78°C, 89%; b) Allyl chloroformate, pyridine, THF, RT, 91%; c) $TiCl_4$, CH_2Cl_2, −78°C, 69%; d) (+)-**11**, 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, toluene, −78°C, 71%; e) Bu_3SnOMe, 70°C, 0.1 torr; f) KF, H_2O, RT; g) CF_3COOH, anisole, CH_2Cl_2, RT, 96% (over three steps); h) $Pd(OAc)_2$, Et_2NH, TPPTS, CH_3CN/H_2O, RT, 99%. DMAP = 4-dimethylaminopyridine, TPPTS = 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt.

(+)-**23** and a diastereoisomer resulting from the concurrent based-induced (NEt_3, DMAP, toluene) isomerization of (+)-**11**. Selective removal of the acetyl group of (+)-**23** was realized by treatment in pure Bu_3SnOMe at 70°C followed by KF/H_2O workup. Subsequent treatment with CF_3COOH

removed the phenylethyl ether giving (+)-**24** (96% yield). Final deprotection and formation of the cyclic acetal ($Pd(OAc)_2$, $HNEt_2$, TPPTS) gave (−)-dolabriferol (−)-**1**; 99% yield), the ^1H and ^{13}C NMR spectra of which were identical to those of natural (−)-**1**. Furthermore, single-crystal X-ray analysis of synthetic (−)-**1** confirmed its structure. As the absolute configurations of the starting dienes **7** and of synthetic intermediates are known, our synthesis of (−)-**1** establishes its absolute configuration to be (2*R*,3*S*,4*S*,5*S*,6*S*,2′*R*,3′*R*,4′*S*).[18]

Polypropionate stereotriads *syn*,*anti*-**6** and *anti*,*anti*-**9** are obtained in one-pot operations starting from inexpensive dienes and enoxysilanes in both their enantiomeric forms. The cyclic hemiacetal subunit (−)-**14** is obtained in four steps starting from diene (−)-**7c**, and the carboxylic acid unit (+)-**11** is prepared in only two steps. Esterification of stereotriad (−)-**22** with (+)-**11** has permitted the first total synthesis of (−)-dolabriferol (10 steps, 7.9% overall yield based on dienes) and has established its absolute configuration.[19] Stereomers of (−)-**1** can be obtained using the same chemistry. For instance, esterification of (−)-**22** with (−)-**11** derived from diene (−)-**7a** has led to (+)-**25** in good yield. The evaluation of the biological activities of (−)-**1** and of its stereoisomers and analogues can now be envisioned.

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