A Key Intermediate towards Oxylipins. A Formal Synthesis of (12*S*)-HETE and (12*S*)-LTB$_4$†

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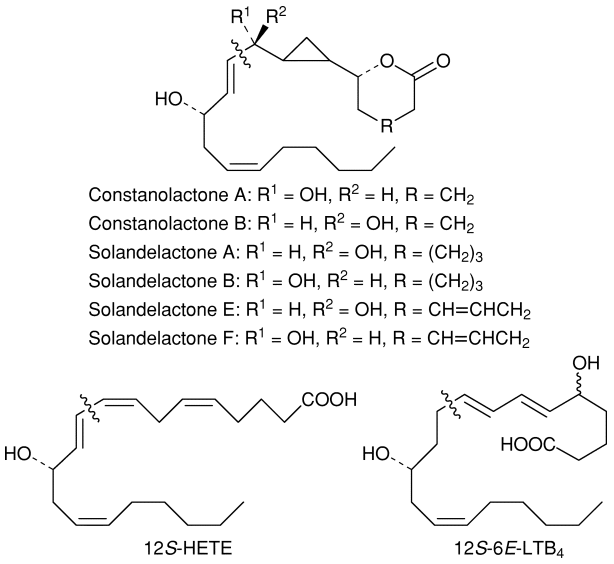
A key intermediate in the synthesis of various oxylipins, the optically active (3*S*,5*Z*)-3-methoxymethoxyundec-5-en-1-yne, has been obtained in 11 steps starting from propane-1,3-diol, with an overall yield of 14%.

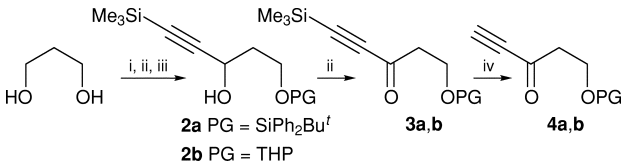
Oxidized metabolites of fatty acid, oxylipins,[1] commonly found in marine organisms,[2] constitute a new, rapidly growing family of natural products. The scarcity of these compounds, their almost unknown biological activity and the fact that a large part of them also belongs to the eicosanoid family,[2] an important class of metabolites involved in mammalian physiology and diseases, are leading to increasing interest in their studies.[1,2,6–8] Engaged in this area,[3,4] we describe here an enantioselective synthesis of (3*S*,5*Z*)-3-methoxymethoxyundec-5-en-1-yne, a key intermediate towards various oxylipins.

Since several oxylipins[5] share a common unit containing *Z* and *E* double bonds as well as an allylic alcohol having the *S* absolute configuration (Scheme 1), a (3*S*,1*E*,5*Z*)-3-hydroxyundeca-1,5-dienyl organometallic would be a convenient reagent for their synthesis. Adding this reagent to a cyclopropyl aldehyde should give access to constanolactones[6] and solandelactones[7] or engaging it in coupling reactions should afford polyenic oxylipins.[8] Such an organometallic compound could be obtained by hydrometallation of the corresponding acetylene *i.e.* (3*S*,5*Z*)-undec-5-en-1-yn-3-ol.



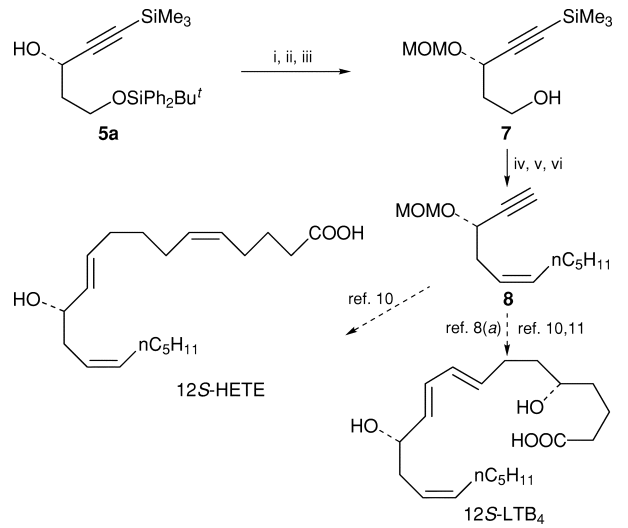
Scheme 1

This optically active (*S*)-prop-2-ynylic alcohol has only been described once in the literature but without details,[9] in contrast to its (*R*)-enantiomer which was obtained after opening a chiral glycidol,[10] sugar modifications[11] or from enzymatic resolution of the corresponding racemic acetate.[9] We devised an alternative route based on asymmetric reduction of ynones[12] which allows for more flexibility in the introduction of the chirality and of various substituents.



Scheme 2 *Reagents*: i, ClSi-Bu^{t}Ph$_2$, NEt$_3$, 4-(dimethylamino)-pyridine (DMAP), CH_2Cl_2 or dihydropyran (DHP), p-TsOH, CH_2Cl_2 (74–60%); ii, DMSO, $(COCl)_2$, NEt$_3$, THF (80–97%); iii, $Me_3SiC{\equiv}CLi$, THF (95–99%); iv, $Na_2B_4O_7$, MeOH–H_2O (90%)

Several ynones bearing different protecting groups have been prepared from propane-1,3-diol using standard chemistry except for the deprotection of the acetylenic function. Carefully controlled conditions were required and sodium borate in aqueous methanol proved to be the perfect reagent affording **4a**–**c** in excellent yields (Scheme 2). These ynones were then submitted to Alpine-borane.[12*b*] The enantiomeric purity of the prop-2-ynylic alcohols so obtained, **5a**–**b**, **6a**–**c**, was determined after converting each one to (3*S*,5*Z*)-undec-5-en-1-yn-3-ol and comparing each optical rotation with the value reported for the known enantiomer.[9,10] As shown in Table 1, ee (enantiomeric excess) varied upon protection or otherwise of the acetylenic and hydroxy functions (entry



Scheme 3 *Reagents*: i, $ClCH_2OCH_3$, NEtPr$^i_2$, DMAP, CH_2Cl_2 (84%); ii, Bu$^n_4$NF, THF (98%); iii, Bu^{n}Li, THF then Me_3SiCl (74%); iv, DMSO, $(COCl)_2$, NEt$_3$, THF (79%); v, $Ph_3P(C_6H_{11}{}^n)^+$, Br^-, sodium hexamethyldisilazide, HMPA–THF (54%). MOMO = methoxymethoxy

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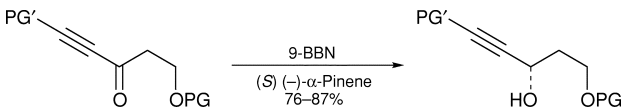
Table 1



Entry	Ynone	PG′	PG	solvent–conc[a]	alcohol	$[\alpha]_D$	ee[b]
1	**3a**	Me_3Si	TBDPS[d]	THF 0.5 M	**5a**	+2°7′	90%
2	**3a**	Me_3Si	TBDPS	THF 2 M	**5a**	+2°3′	76%
3	**4a**	H	TBDPS	THF 0.5 M	**6a**	–3°7′	81%
4	**4a**	H	TBDPS	Neat	**6a**	–2°3′	50%
5	**3b**	Me_3Si	THP[d]	THF 0.5 M	**5b**	–13°3′	36%
6	**4b**	H	TBDPS	THF 0.5 M	**6b**	–8°	21%
7	**4c**	H	H	THF 0.5 M	**6c**	—[c]	—[c]

[a]Ynone concentration; [b]see text for ee determination; [c]no transformation; [d]TBDPS = $SiBu^tPh_2$; THP = tetrahydropyran-2-yl; 9-BBN = 9-borabicyclo[3.3.1]nonane.

1 *vs.* 3, 5 *vs.* 6), *and* upon the nature of the remote hydroxy protecting group (entries 5–6 *vs.* 1–4). The striking effect‡ of the remote protecting group may be due to competition for borane coordination.

The protected pent-4-yne-1,3-diol **5a**, obtained with a reasonable optical purity,§ was further elaborated to the required oxylipin synthon as shown in Scheme 3. Two steps proved to be critical in this sequence: the oxidation of the free primary alcohol **7** prone to β-elimination and the exclusive formation of the *Z* double bond achieved *via* a 'salt free' Wittig reaction.[3] Desilylation eventually gave the required terminal acetylene **8**. since its (*R*)-enantiomer has been used in the synthesis of (12*R*)-HETE[10] as well as LTB_4,[8a,10,11] the present synthesis constitutes a formal synthesis of their enantiomers, *i.e.* (12*S*)-LTB_4 and (12*S*)-HETE, the latter being present in marine organisms.[5c,5a]

Experimental

NMR spectra were recorded on a Bruker AC-250. *J* values are in Hz. IR spectra were recorded on a Spectrafile IR Plus MIDAC spectrometer. Mass spectra were measured on a Jeol D300 (70 eV) mass spectrometer. Solvents and the usual reagents were dried and purified by conventional methods.

Desilylation. 5-tert-*Butyldiphenylsilyloxypent*-1-*yn*-3-*one* **4a**.—To a solution of **3a** (4.6 g, 11.27 mmol) in methanol (80 ml) was added a 0.01 M aqueous borax solution (25 ml). After 30 min at room temperature, the mixture was chilled to 0 °C then treated with 10% HCl aqueous solution (20 ml). After methanol evaporation, the mixture was extracted with diethyl ether (3 × 60 ml), the organic phase was then dried and concentrated yielding a clear oil which was purified by flash chromatography. δ_H 1.07 (9H, s), 2.83 (2H, t, *J* 6.1), 3.22 (1H, s), 4.06 (2H, t, *J* 6.1), 7.43 (6H, m), 7.70 (4H, m); δ_C 19.15 (s), 26.70 (q), 48.12 (t), 59.02 (t), 78.74 (s), 81.39 (d), 127.68 (d), 129.72 (d), 133.28 (s), 135.55 (d), 185.54 (s); ν/cm^{-1} ($CHCl_3$): 3280, 2090, 1670; *m*/*z* (%): 279 (11), 278 (63), 248 (10), 206 (100), 200 (41).

Data for (3S,5Z)-3-*methoxymethoxyundec*-5-*en*-1-*yne* **8**.—$[\alpha]_D^{20}$ –106 (*c* = 0.85, CH_2Cl_2); δ_H 0.91 (3H, t, *J* 7), 1.25–1.45 (6H, m), 2.07 (2H, td, *J* 7.0, 7.0), 2.42 (1H, d, *J* 1.9), 2.50 91H, dd, *J* 6.2, 0.5), 2.53 (1H, dd, *J* 6.9, *J* 0.5), 3.41 (3H, s), 4.33 (1H, ddd, *J* 6.6, 6.6, 1.9), 4.61 (1H, d, *J* 6.7), 4.93 (1H, d, *J* 6.7), 5.42 (1H, dtt, *J* 10.8, 6.6, *J* 1.6), 5.59 (1H, dtt, *J* 10.8, 6.2, 1.6); δ_C 14.02 (q), 22.50 (t), 27.41 (t), 29.16 (t), 31.45 (t), 33.52 (t), 55.59 (d), 65.22 (q), 73.49 (d), 82.31 (s), 94.09 (t), 123.58 (d), 133.22 (d). ν/cm^{-1} ($CHCl_3$): 3290, 2080; *m*/*z* (%): 211 (M^++1, <1), 124 (46), 99 (100), 96 (42), 91 (47), 82 (68), 68 (75), 55 (52). Found: C, 74.54; H, 10.29, $C_{13}H_{22}O_2$ requires C 74.28; H 10.47%.

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References

1 W. H. Gerwick, *Chem. Rev.*, 1993, **93**, 1807.
2 W. H. Gerwick and M. W. Bernart, Eicosanoids and related compounds from marine algae, in *Marine Biotechnology, Vol. I: Pharmaceutical and bioactive natural products*, ed. D. H. Attaway and O. R. Zaborsky, Plenum, New York, 1992, p. 101.
3 D. Grandjean, P. Pale and J. Chuche, *Tetrahedron*, 1991, **47**, 1215.
4 A. Benkouider, PhD Thesis, 1994, University of Reims-Champagne-Ardenne, Reims; C. Barloy-Da Silva, PhD Thesis, 1998, University L. Pasteur, Strasbourg.
5 (*a*) Constanolactones: D. G. Nagle and W. H. Gerwick, *J. Org. Chem.*, 1994, **59**, 7227; *Tetrahedron Lett.*, 1989, **31**, 2995; (*b*) Solandelactones: Y. Seo, K. W. Cho, J.-R. Rho, J. Shin, B.-M. Kwon, S.-H. Bok and J.-I. Song, *Tetrahedron*, 1996, **52**, 10583; (*c*) 12 S-HETE and 6E-LTB4: M. W. Bernart and W. H. Gerwick, *Phytochemistry*, 1994, **36**, 1233.
6 For other synthetic approaches towards these lactones, see: S. Varadarajan, D. K. Mohapatra and A. Datta, *Tetrahedron Lett.*, 1998, **39**, 5667; H. Miyaoka, T. Shigemoto and Y. Yamada, *Heterocycles*, 1998, **47**, 415; J. D. White and M. S. Jensen, *J. Am. Chem. Soc.*, 1995, **117**, 6224; T. Nagasawa, Y. Onoguchi, T. Matsumoto and K. Suzuki, *Synlett*, 1995, 1023.
7 For another approach towards these lactones, see: S. Varadarajan, D. K. Mohapatra and A. Datta, *Tetrahedron Lett.*, 1998, **39**, 1075.
8 For related synthesis of eicosanoids, see: (*a*) D. Chemin and G. Linstrumelle, *Tetrahedron*, 1992, **48**, 1943; (*b*) K. C. Nicolaou, J. Y. Ramphal, N. A. Petasis and C. N. Serhan, *Angew. Chem., Int. Ed.*, 1991, **30**, 1100.
9 M. Treilhou, A. Fauve, J.-R. Pougny, J. C. Promé and H. Veschambre, *J. Org. Chem.*, 1992, **57**, 3203.
10 K. C. Nicolaou, J. Y. Ramphal and Y. Abe, *Synthesis*, 1989, 898.
11 P. Pianetti, P. Rollin and J.-R. Pougny, *Tetrahedron Lett.*, 1986, **27**, 5853.
12 (*a*) H. C. Brown and P. V. Ramachandran, *Acc. Chem. Res.*, 1992, **25**, 16; (*b*) M. M. Midland, A. J. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tsai and D. B. Cardin, *Tetrahedron*, 1984, **40**, 1371; M. M. Midland and R. S. Graham, *Org. Synth.*, 1984, **63**, 57; (*c*) C. Helal and E. J. Corey, *Tetrahedron Lett.*, 1995, **36**, 9153; (*d*) C. J. Helal, P. A. Magriotis and E. J. Corey, *J. Am. Chem. Soc.*, 1996, **118**, 10938.

‡A remote steric effect across a C–C triple bond was recently observed in another enantioselective reduction: see ref. 12(*d*).
§The ees obtained are similar to the highest described for related compounds.[12a,b]