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Allylic Alcohol Transposition by Ortho Ester-Initiated Carbonate Extension. Synthesis of the Vasodilator 11(*R*),12(*S*),15(*S*)-Trihydroxyeicosa-5(*Z*),8(*Z*),13(*E*)-trienoic Acid

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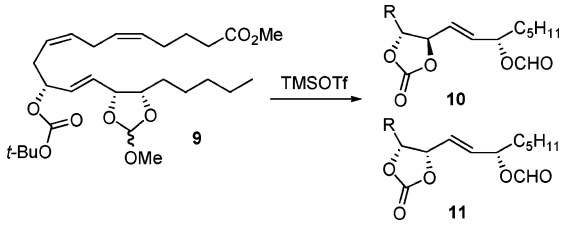
ABSTRACT



The title compound 1 was obtained via methyl ester 2, which was synthesized in four steps from an isomeric 11,14,15-triol ester 5. In the key step, Boc orthoformate 9 was treated with TMS triflate to initiate intramolecular nucleophilic substitution with allylic transposition, forming cyclic carbonates 10 and 11.

In the course of research on endogenous mammalian vasomodulators in the laboratories of Falck and Campbell, a potent vasodilator was discovered in rabbit aortic endothelium and identified as 11(*R*),12(*S*),15(*S*)-trihydroxyeicosa-5(*Z*),8(*Z*),13(*E*)-trienoic acid (**1**, Figure 1).[1] Compound **1** is a member of a class of triol acids, designated THETAs, that are biosynthesized from arachidonic acid by a sequence of lipoxidation to the hydroperoxide 15-HPETE, isomerization to an epoxy alcohol, and hydrolysis. The 11,12,15-triol pattern of **1** was deduced by mass spectral analysis, but because of the scarcity of the natural product, assignment of stereochemistry awaited comparison with synthetic material. To that end, Falck and co-workers synthesized the four C11−C12 diastereomers of structures **1** and **2** from stereodefined vicinal diol subunits.[1] Herein is reported a concise synthesis of **1** from the known 11,14,15-triol ester **5**,[2] in which transposition of the C12−C14 allylic alcohol array was accomplished by a new cationic ScN′ reaction[3] initiated by a cyclic ortho ester[4] and terminated by a *t*-butyl carbonate.[5,6]

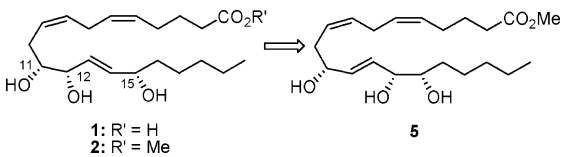


Figure 1. Synthetic plan.

Triol ester **5** was obtained in two steps from 15(*S*)-HETE methyl ester (**3**) as described earlier by Falck (Scheme 1).[2]

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(2) Falck, J. R.; Manna, S.; Siddhanta, A. K.; Capdevila, J.; Buynak, J. D. *Tetrahedron Lett.* **1983**, *24*, 5715.

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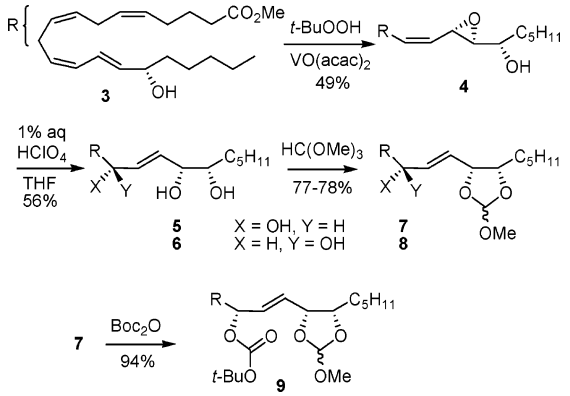
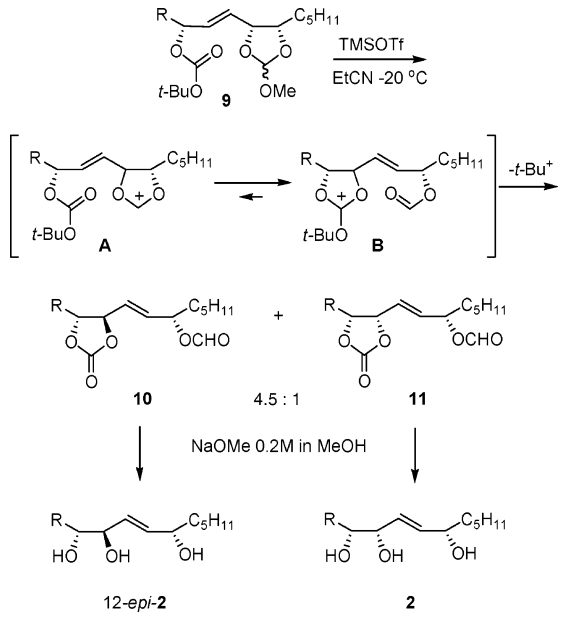
Scheme 1. Preparation of Boc Orthoformate **9**



Epoxidation of **3** on a 3.5-g scale[7] afforded the anti (erythro) epoxy alcohol **4** (49%) plus its syn (threo) diastereomer (21%). Hydrolysis of **4** provided triol **5** and its more polar epimer **6** (∼1:1). Treatment of the separated triols with excess $HC(OMe)_3$ and catalytic PPTS in dichloromethane gave orthoformates **7** and **8**, plus bisorthoformates from which the 11-OH group could be released by titration of the reaction mixtures with methanol.[8] In this way, **7** and **8** were obtained reproducibly in 77−78% yield from **5** and **6**. The C11 configurations were assigned at this stage by *O*-methylmandelic ester analysis.[9] The 11*R* epimer **7** was converted to *t*-butyl carbonate **9** in 94% yield by treatment with Boc_2O, *i*-Pr_2NEt, and DMAP in 2:1 hexane−diethyl ether.[10]

Reaction of **9** (275 mg) with TMSOTf in EtCN at −20 °C gave trans cyclic carbonate **10** and its cis epimer **11** (4.5:1) in 62% yield (Scheme 2). The useful desformyl congeners were also obtained in 6% yield. The Boc derivative of **8** likewise delivered a 5.7:1 trans/cis product mixture in comparable yield. Propionitrile (mp −93 °C) was chosen instead of acetonitrile to enable experimentation at lower temperature without resorting to the use of mixed solvents.[5b] In trials at −78 °C, little formation of **10**/**11** was observed. The ring stereochemistry was evident from the chemical shifts of H11 and H12 (**10**: δ 4.32, 4.70; **11**: 4.71, 5.13).[11] The H13 and H14 signals at δ 5.7−5.9 were well isolated at 600 MHz and showed J = 15.6 Hz, characteristic of the *E* configuration.

Scheme 2. Ionization of **9** Leading to Cyclic Carbonates and Methanolysis Affording Transposed Triols



Exposure of the separated carbonates **10** and **11** to methanolic NaOMe afforded 12-*epi*-**2** and **2** (86−90%), whose ^1H and ^{13}C NMR spectra agreed with those of the 11*R* product pair synthesized by Falck.[1] The H11 resonances occurred at δ 3.53 and 3.71, respectively, consonant with the assigned syn and anti C11−C12 relationships.[12] Saponification[1] of **2** yielded acid **1**, which by negative-ion ESI/MS/MS showed a diagnostic *m*/*z* 197 ion arising from C11/C12 cleavage; in the spectrum of the acid corresponding to **5**, there appeared instead an *m*/*z* 223 ion attributable to C13/C14 cleavage.[13]

The genesis of 1,3-dioxolan-2-yl cations by ionization of ortho esters, as depicted in Scheme 2 for the reaction **9**→**A**, is well documented.[4] Subsequent nucleophilic capture with ring opening typically leads to vicinally functionalized products such as bromohydrin esters. An orthoformate linked to a phenolic group gave the bromo formate when treated with AcBr but cyclized to the chromane under catalysis by PPTS, demonstrating the influence of the counterion on inter- vs intramolecular reactivity.[4c] Here, the latter mode prevails by isomerization of **A** to **B**, which is formulated as an

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(6) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798.

(7) For procedures applicable to the synthesis of **3** on a multigram scale, see: (a) Iacazio, G.; Langrand, G.; Baratti, J.; Buono, G.; Triantaphylidès, C. *J. Org. Chem.* **1990**, *55*, 1690. (b) Martini, D.; Iacazio, G.; Ferrand, D.; Buono, G.; Triantaphylidès, C. *Biocatalysis* **1994**, *11*, 47.

(8) (a) The ratio of exo/endo methoxy epimers, initially 1:4, changes to 3:1 during this methanol treatment, paralleling the behavior of nucleosidic orthoformates: Bhat, G. A.; Townsend, L. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2387. (b) Maillard, M. C.; Nikodijevic, O.; LaNoue, K. F.; Berkich, D.; Ji, X.-d.; Bartus, R.; Jacobson, K. A. *J. Pharm. Sci.* **1994**, *83*, 46. (c) For a comparison of hydrolysis rates of acyclic vs six-membered cyclic ortho esters, see: Deslongchamps, P.; Dory, Y. L.; Li, S. *Tetrahedron* **2000**, *56*, 3533.

(9) (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569.

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(12) Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org. Lett.* **2001**, *3*, 2981.

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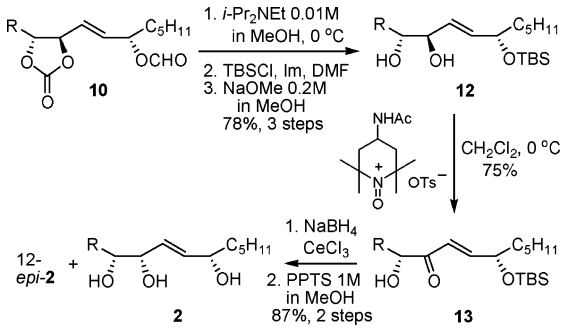
equilibrium driven forward by charge dispersal. Related iodocyclizations of homoallylic *t*-butyl carbonates have shown evidence of stereochemical equilibration prior to departure of the *t*-butyl cation, as the less sterically hindered diastereomer predominated in all cases.[5] The same products also appear to be kinetically favored on the basis of results of low-temperature experiments.[5] The preponderant formation of trans carbonates in the present work accords with these precedents.

In Bartlett's studies on carbonate extension, acetonitrile was found to play a critical role by trapping the *t*-butyl cation as the Ritter intermediate; in turn, this species proved able to transfer *t*-Bu^+ to dimethylformamide.[5a] Plausibly, similar transfers could impact the reaction of **9**→**10/11**, e.g., by participation of the solvent as a cation shuttle; adjuvant trapping agents such as anisole might therefore be enlisted to assess the nature and extent of such effects.

To augment the supply of the anticonfigured triol **2**, a method was devised to utilize the major carbonate **10** by inversion at C12 (Scheme 3). Syn diol **12** was obtained from **10** by a sequence of deformylation, silylation, and carbonate cleavage. Exposure of **12** to the oxidant formed from 4-acetamido-TEMPO and *p*-TsOH·H_2O[14] then delivered enone **13** in 75% yield. The compatibility of this oxidizing system with acid-sensitive functionality can be attributed to the low solubility of *p*-TsOH in CH_2Cl_2.[14b] Luche reduction of **13** at −50 °C was followed by cleavage of the *t*-butyldimethylsilyl ether to provide triols **2** and 12-*epi*-**2** in a 3.5:1 ratio.[15] No attempt was made to identify optimal conditions for this reduction.

In summary, the key features of this synthesis include utilization of the differential solvolytic lability of acyclic and cyclic orthoformates[8] to access intermediate **9**, deployment of a new 1,3-dioxolan-2-yl cation-mediated ScN′ reaction to effect allylic transposition, and processing of the diastereomeric carbonates **10** and **11** to converge on the penultimate target **2**.

Scheme 3. Inversion at C12



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Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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