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Synthesis of Resolvin D6 and the Silyl Ether of the Resolvin E2 Methyl Ester via *trans*-Enynyl Alcohols

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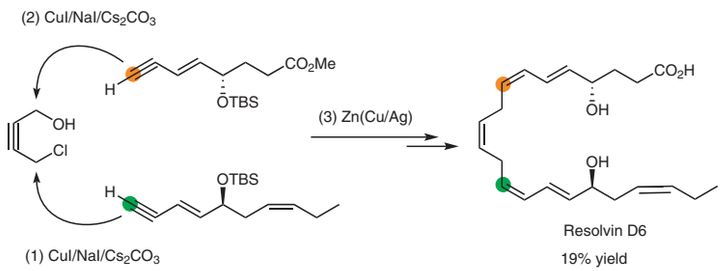

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Abstract Two *trans*-enynyl alcohol intermediates corresponding to the C1–C8 and C13–C22 parts of resolvin D6 (RvD6) were prepared through the Hudrlik–Peterson reaction of the TMS-substituted *trans*-epoxy alcohols with TMS-acetylide and subsequent TMS-desilylation. These intermediates were coupled with a 1,4-dihalo-2-butyne derivative under copper catalysis, and the resulting acetylene was reduced with Zn(Cu/Ag) to afford the TBS ether of RvD6 methyl ester. Desilylation with TBAF yielded the γ-lactone of RvD6, which was hydrolyzed to RvD6. The total yield of RvD6 was 1.9% in 19 steps from (3-trimethylsilyl)propargyl alcohol. The TBS ether of RvE2 methyl ester was also synthesized.

Key words resolvin D6, resolvin E2, stereoselective synthesis, epoxide ring opening, semi-hydrogenation, zinc, enynes

Hydroxy metabolites of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), including resolvins, show anti-inflammatory and pro-resolution activities.[1] Because they are available only in minute quantities by enzymatic conversion and/or in limited quantities from commercial sources, organic syntheses have been developed.[2] However, synthesis of several resolvins, especially newly isolated resolvins, remains undeveloped, and thus fundamental biological investigations such as the structure and activity relationships are unexplored. The *E*,*Z*-dienyl alcohol unit is found in several metabolites and has been constructed by several methods. Resolvins D6 and E2 (abbreviated as RvD6 and RvE2, respectively) each possess two such units[3,4] which are connected through the butenyl bridge (Figure 1). A few organic syntheses of these metabolites have been developed.[5,6] However, yields in the synthesis of RvD6 were not fully reported,[5] and RvD6 is not commercially available.

To improve the availability of RvD6, the synthesis of RvD6 was started and the established method was then applied to the synthesis of RvE2.

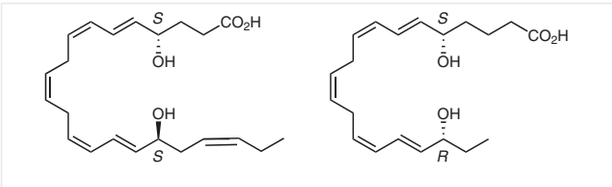
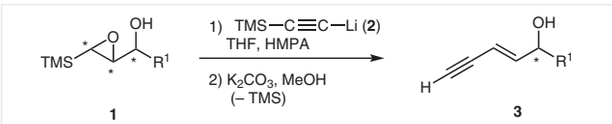


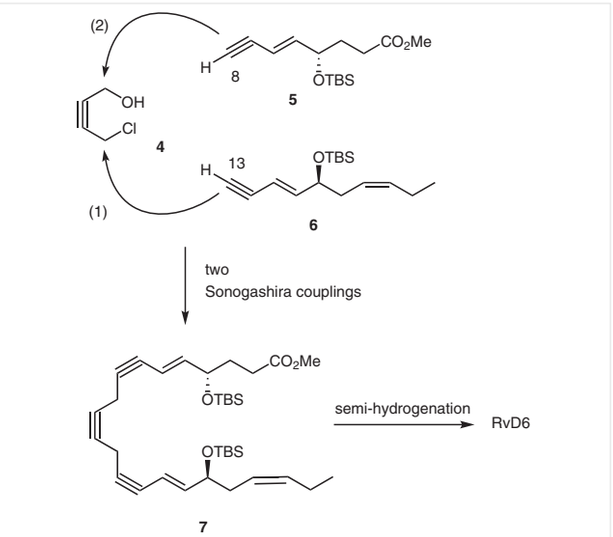
Figure 1 Resolvins D6 and E2

Recently we reported[7] the Hudrlik–Peterson reaction of the TMS-substituted *trans*-epoxy alcohols **1** with TMS-acetylide **2** followed by TMS-desilylation to afford *trans*-enynyl alcohols **3** (Scheme 1). These transformations were used as the key steps for the syntheses of 18-HEPE[7] and an intermediate of resolvin D1.[8] As the next target we chose RvD6, envisaging that the central part would be synthesized by connecting two intermediates, **5** and **6**, to 1,4-dihalo-2-butyne derivative **4**[9] by the copper-catalyzed couplings followed by semi-hydrogenation as delineated in Scheme 2. Herein, we report a synthesis of RvD6 along this strategy and its application to the formal synthesis of RvE2.



Scheme 1 New standard for the synthesis of *trans*-enynyl alcohols

The epoxy and allylic alcohols **8** and **11** were synthesized according to a reported procedure[10] through the Sharpless asymmetric epoxidation of the racemic alcohol

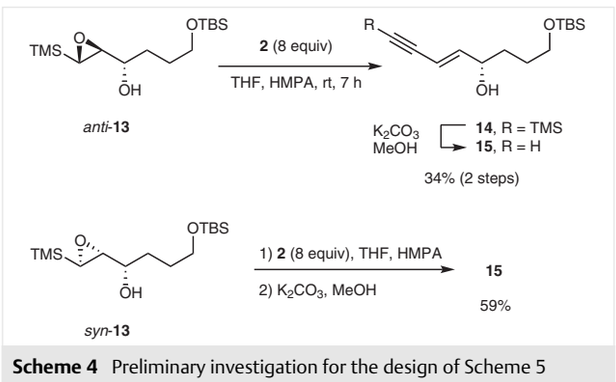


Scheme 2 Strategy for the synthesis of RvD6

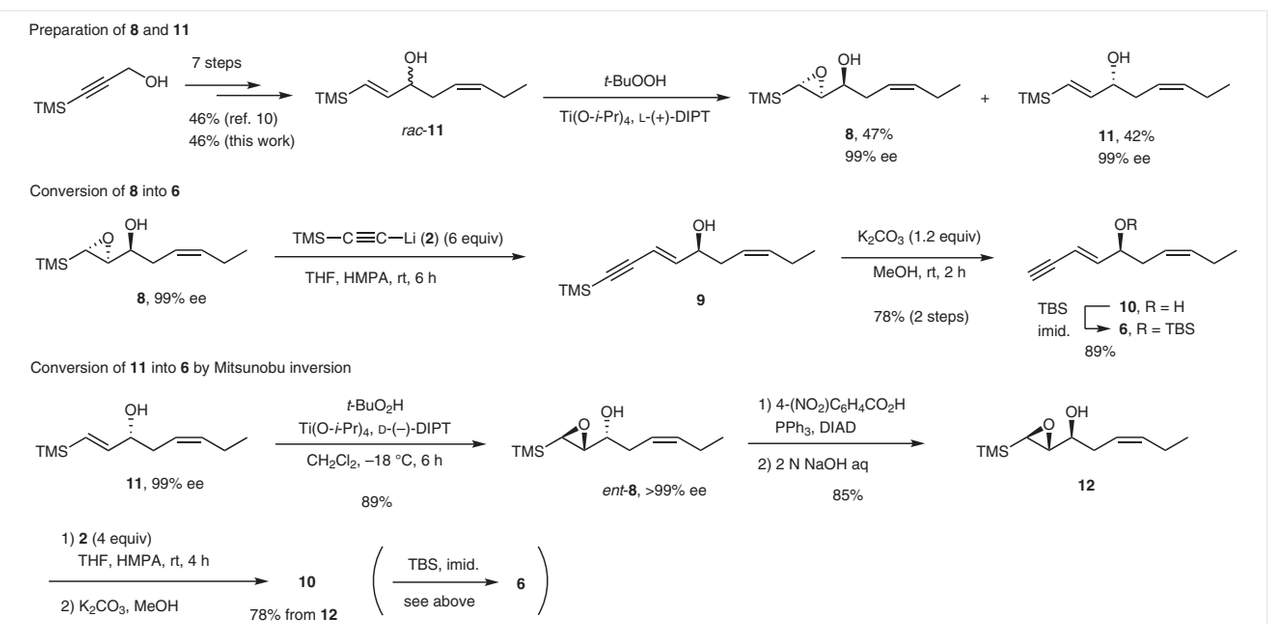
rac-**11** with *t*-BuO_2H and Ti(O-*i*-Pr)$_4$/L-(+)-DIPT (Scheme 3). As reported[7] earlier, the Hudrlik–Peterson reaction of **8** by using the racemate corresponding to **8**, proceeded well to afford *trans*-enynyl alcohol **9**, which was then subjected to TMS desilylation to afford alcohol **10** in 78% yield from **8**. Then, TBS protection afforded the C13–C22 intermediate **6** in 89% yield.

Allylic alcohol **11** was converted to *ent*-**8** by the Sharpless asymmetric epoxidation with use of D-(–)-DIPT. The increased enantiopurity (>99% ee) was the result of the kinetic resolution between **11** and *ent*-**11** at a ratio of 99.5:0.5. The Mitsunobu inversion afforded *syn*-epoxy alcohol **12** in 85% yield. The Hudrlik–Peterson reaction of **12** with acetylide **2** at room temperature was complete within four hours to afford **10** in 78% yield.

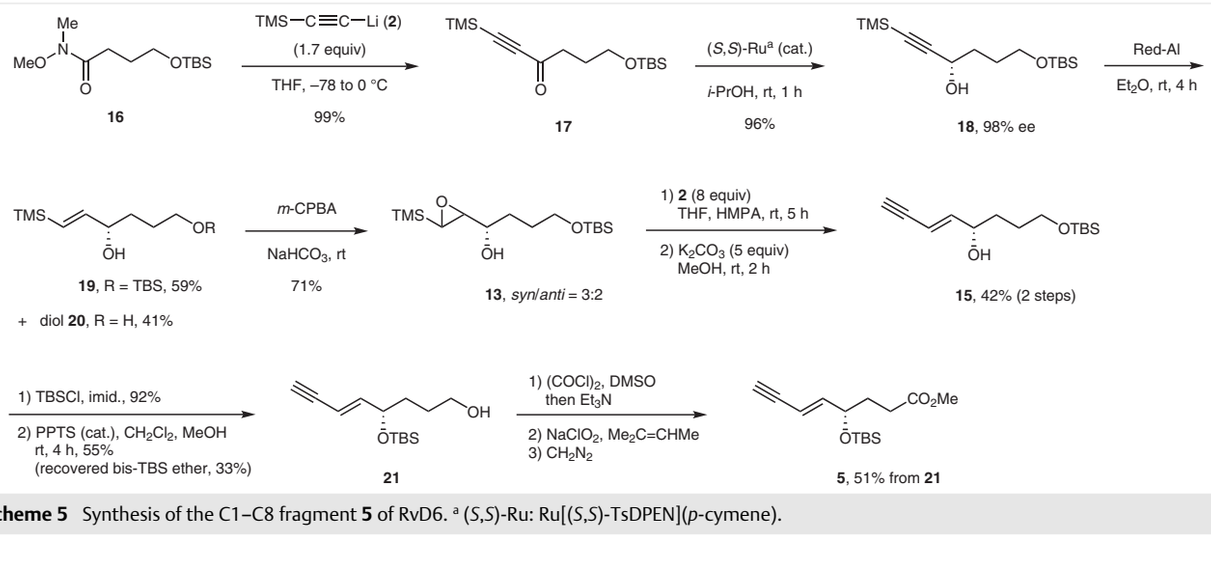
Next, the above strategy, including the Sharpless asymmetric epoxidation followed by the Hudrlik–Peterson reaction, was applied to the synthesis of the C1–C8 intermediate **5**. The reaction of the *anti*-epoxy alcohol *anti*-**13**, a product of the Sharpless asymmetric epoxidation, followed by the removal of TMS in **14**, gave **15** in only 34% yield (Scheme 4). In contrast, the yield of **15** from *syn*-**13** was 59%. In consideration of these yields and the two additional steps for the Mitsunobu inversion of *anti*-**13** to *syn*-**13** in 83% yield, a *syn*-rich mixture of *syn*- and *anti*-epoxy alcohols **13** was synthesized by a different method for the Hudrlik–Peterson reaction (Scheme 5).



Scheme 4 Preliminary investigation for the design of Scheme 5



Scheme 3 Synthesis of the C13–C22 fragment **6** of RvD6

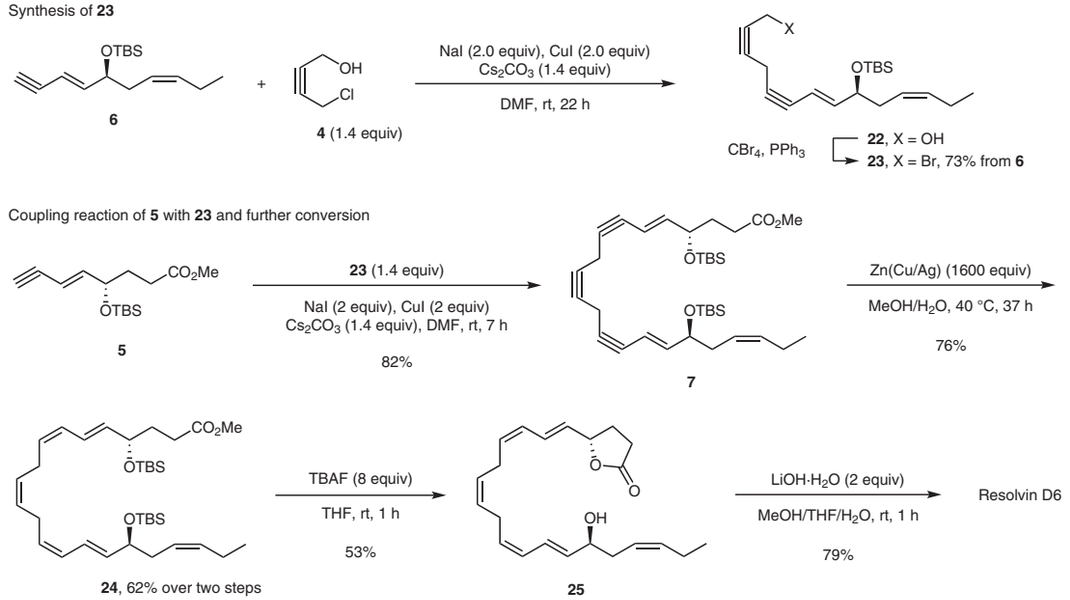


Scheme 5 Synthesis of the C1–C8 fragment **5** of RvD6. [a] (*S*,*S*)-Ru: Ru[(*S*,*S*)-TsDPEN](*p*-cymene).

The Weinreb amide **16** synthesized from γ-butyrolactone[11] was converted to acetylene ketone **17**, which was reduced by using the Noyori catalyst[12] to propargylic alcohol **18** with 98% ee as determined by chiral HPLC analysis.

Red-Al reduction of **18** gave a mixture of **19** and diol **20** in 59% and 41% yield, respectively. After separation by routine chromatography, epoxidation of **19** with *m*-CPBA gave a mixture of *syn* and *anti* isomers of **13** in a 3:2 ratio, and the Hudrlik–Peterson reaction with TMS-acetylide **2** followed by TMS-desilylation gave **15** in 42% yield. Protection of **15** with TBSCl followed by regioselective deprotection of the bis-TBS ether afforded **21** in 55% yield. Finally, two-step oxidation of **21** to the acid followed by esterification gave **5** in 51% yield.

The last stage of the synthesis of RvD6 is delineated in Scheme 6, in which both intermediates **6** and **5** were joined to **4**[9] by copper-catalyzed coupling to construct the entire structure of RvD6. The coupling of **6** with **4** was followed by bromination of alcohol **22** to afford **23** in 73% yield. The second coupling reaction, carried out between acetylene **5** and bromide **23**, produced acetylene **7**, which was chemically unstable to some extent. We envisaged a Zn(Cu/Ag)-assist-



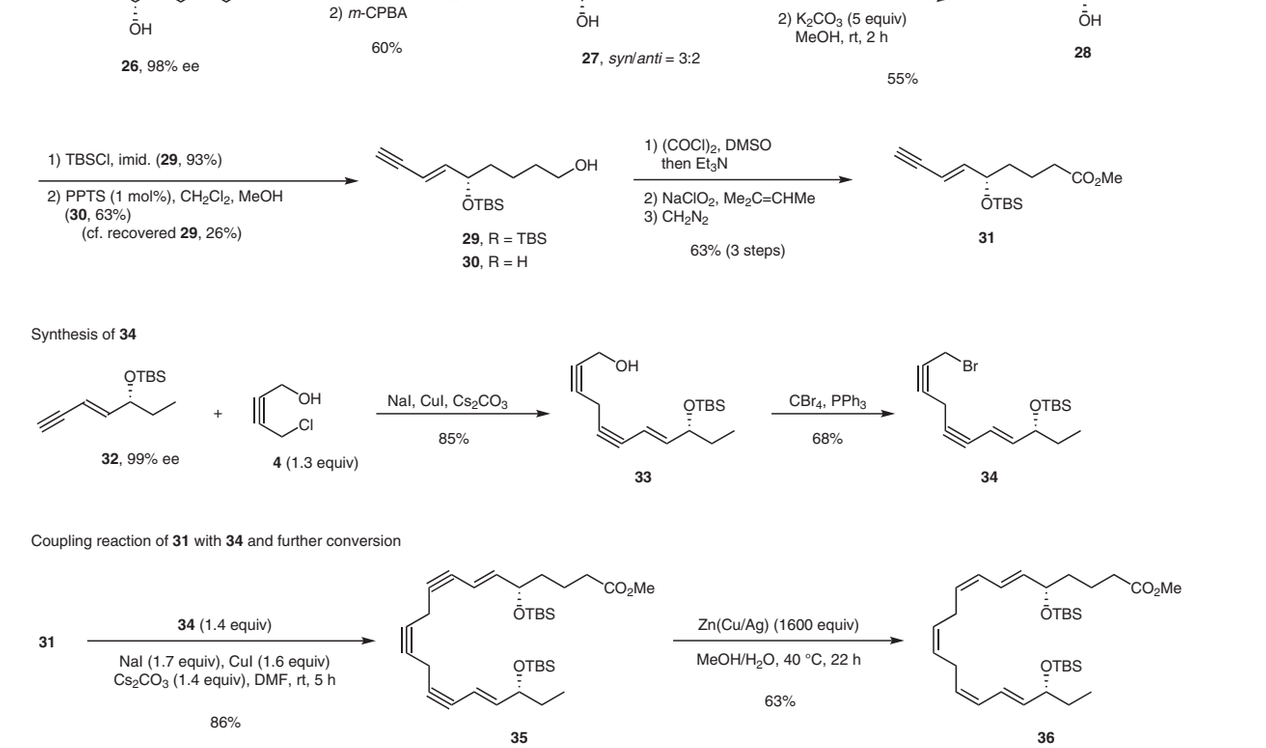
Scheme 6 Final stage of the synthesis of RvD6

ed reduction[13] of the conjugated acetylene followed by a reduction of the nonconjugated acetylene using P-2 Ni[14] under H_2 because Zn(Cu/Ag) was reported not to reduce the nonconjugated acetylene.[13] However, we observed that an isolated acetylene in an intermediate for the synthesis of RvE2 could be reduced by using a large excess of Zn(Cu/Ag).[15] According to this protocol, reduction of **7** was conducted with a large excess of Zn(Cu/Ag) (about 1600 equiv) to produce **24** in 62% yield from **5**. Fortunately, removal of Zn(Cu/Ag) by filtration through Celite was not an operational problem. Desilylation of **24** was carried out with TBAF. However, dihydroxy ester of RvD6 and/or RvD6 was not isolated. Instead, hydroxy lactone **25** was obtained in 53% yield. Finally, hydrolysis with LiOH afforded RvD6 in 79% yield.

The ^1H and ^{13}C NMR spectral data in CD_3CN were identical to those reported previously.[5] In addition, the ^1H and ^{13}C–APT NMR spectra in CD_3OD and UV spectra with ε were consistent with the structure of RvD6.

In a similar manner, **36**, the literature precursor to RvE2,[6c] was synthesized as summarized in Scheme 7. The starting propargylic alcohol **26** with 98% ee was synthesized from the corresponding ketone and converted to a diastereomeric mixture of epoxy alcohol **27**, which upon the Hudrlick–Peterson reaction followed by TMS-desilylation produced **28** in 55% yield (two steps). The functional groups of **28** were then manipulated to afford **31** in five steps via **29** and **30**. Enyne **32** was the previous product of the Hudrlick–Peterson reaction,[7] and was coupled with **4** to produce **33**, which was then converted to bromide **34**. The coupling of **31** with **34** proceeded well, and the semi-hydrogenation of the resulting acetylene **35** by using a large excess[15] of Zn(Cu/Ag) afforded **36** in 63% yield. There was no contamination with over-reduced products. The ^1H and ^{13}C NMR spectra of **36** were in good agreement with the reported values.[6c]

In summary, we have applied the Hudrlick–Peterson reaction to the synthesis of RvD6.[16] The semi-hydrogenation of three triple bonds including one isolated triple bond was achieved by using a large excess of Zn(Cu/Ag), thereby simplifying the synthesis. A total yield of RvD6 in the longest linear sequence through **11**, **6**, and **23** was 1.9% in 19 steps from (3-trimethylsilyl)propargyl alcohol. The same procedure was then successfully applied for the synthesis of the bis-TBS ether of the RvE2 methyl ester. The procedure pro-



Scheme 7 Synthesis of the RvE2 intermediate

vided in the Supporting Information will be useful for reproducing the synthesis.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611826.

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(15) Reduction of **35** to **36** at 30 °C or 40 °C for 24 h is summarized in the Supporting Information (page S2).
(16) **Synthesis of (*S*,*E*)-1-[(*tert*-Butyldimethylsilyl)oxy]oct-5-en-7-yn-4-ol (15)**
To a solution of trimethylsilylacetylene (0.43 mL, 3.05 mmol) in THF (0.3 mL) was added dropwise *n*-BuLi (1.70 mL, 2.67 mmol, 1.57 M in hexane) at –78 °C. After 15 min of stirring at rt, HMPA (0.69 mL, 3.97 mmol) and a solution of epoxy alcohol **13** (100 mg, 0.331 mmol) in THF (0.15 mL) were added. The solution was stirred at rt for 5 h and then diluted with saturated NH_4Cl. The product was extracted with EtOAc and passed through a short column of silica gel for the next reaction. A mixture of the above enyne and K_2CO_3 (212 mg, 1.53 mmol) in MeOH (1 mL) was stirred at rt for 2 h and then diluted with saturated NH_4Cl. The product was extracted with EtOAc and purified by chromatography on silica gel to give alcohol **15** (34 mg, 42% over two steps); colorless oil; R_f = 0.37 (hexane/EtOAc, 4:1); $[\alpha]_D^{20}$ –22 (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.90 (s, 9 H), 1.53–1.80 (m, 4 H), 2.87 (d, *J* = 2.1 Hz, 1 H), 3.25 (d, *J* = 4.0 Hz, 1 H), 3.66 (t, *J* = 5.2 Hz, 2 H), 4.16–4.25 (m, 1 H), 5.74 (dt, *J* = 16.0 Hz, 2.1 Hz, 1 H), 6.25 (dd, *J* = 16.0 Hz, 5.4 Hz, 1 H). ^{13}C–APT NMR (75 MHz, $CDCl_3$): δ = –5.4 (+), 18.4 (–), 26.0 (+), 28.6 (–), 34.6 (–), 63.5 (–), 71.3 (+), 77.6 (–), 82.0 (–), 108.3 (+), 147.9 (+). HRMS–FAB$^+$: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}O_2Si$: 255.1780; found: 255.1782.