Titanium(II)-based *Z*-reduction of alkynes: stereo- and regio-specific *Z*-dideuteriation of conjugated and methylene-skipped ynes

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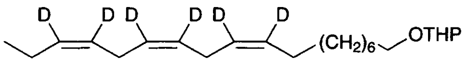
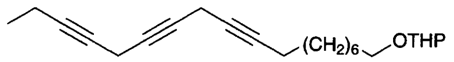
A Ti^{II}-mediated, stereo- and regio-specific reduction of isolated, conjugated and methylene skipped poly-ynes to the corresponding *Z*-dideuterio polyenes in a one-pot procedure with D_2O as deuterium source is described, and this methodology (using H_2O) is applied to the synthesis of (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trienyl acetate, the major sex attractant of *Scrobipalpuloides absoluta*, a destructive pest of tomatoes.

Fruit-fly biosynthetic work required the ^{2}H-labelled, methylene-skipped triene system **1**,[1] and reduction of the skipped triyne **2** appeared to be a direct approach to **1**, particularly as **2** and related compounds are accessible by metal-mediated coupling of alk-1-ynes and prop-2-ynylic halides.[2] However, a survey of reduction methods indicated that several problems could arise in the reduction of **2** to **1**, and some methods utilise inconvenient or expensive sources of deuterium. Very recently, Meinwald[3] employed deuterioboration followed by deuterio-acid cleavage of the vinyl borane, to acquire labelled linolenic acid, and concluded this was the best of existing methods for the *cis*-reduction of alkynes, without ^{2}H-scrambling. In view of the importance of stereo- and regio-specifically labelled polyunsaturated long chain acids in biosynthetic studies,[4] we report that *Z*-dideuteriation of poly-yne systems, both conjugated and methylene-skipped, is conveniently achieved by a Ti^{II}-mediated method. Exploratory investigations were conducted with Me_3Si-protected skipped diyne **3** which on treatment with Ti(OPr^i)$_4$ and *ca.* 2 equiv. of the reducing Grignard reagent Pr^{i}MgBr, in ether at −70 °C followed by H_2O quenching, conventional work up and flash chromatography yielded **4** in 53% yield. GC–MS examination indicated one isomer was formed and analysis of the 500 MHz ^{1}H NMR spectrum confirmed the Z,Z-configuration of the skipped diene. [In vinyl silanes, typical ^{1}H–^{1}H coupling constants (^3J) are 18–19 Hz for *E*- and 14 Hz for *Z*-configured systems].[5] Use of D_2O for quenching provided the tetradeuterio derivative **5** which exhibited only the expected four signals in the ^{2}H NMR spectrum at δ 6.25, 5.53, 5.43 and 5.35 relative to $CDCl_3$ at δ 7.24.



1



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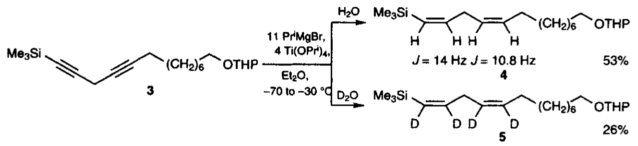
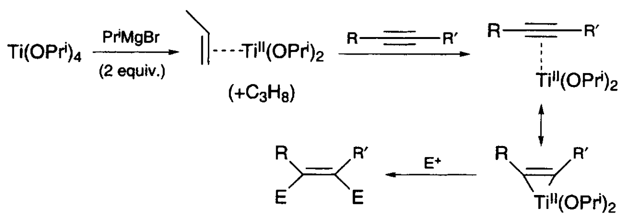


Scheme 1



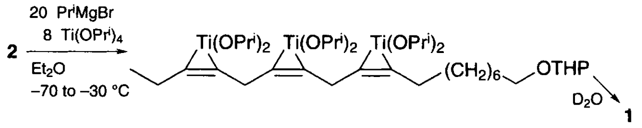
Scheme 2

Based on the earlier suggestions of Kulinkovich, and Sato's proposal of alkyne–Ti^{II} complexation,[6] the reaction probably proceeds as shown in Scheme 2 with the alkyne displacing propene from the η^2-propene–Ti^{II} complex, to form a species with titanacyclopropene characteristics that experiences formal electrophilic cleavage with retention of configuration at both bonds to yield *Z*-alkene products.[7]

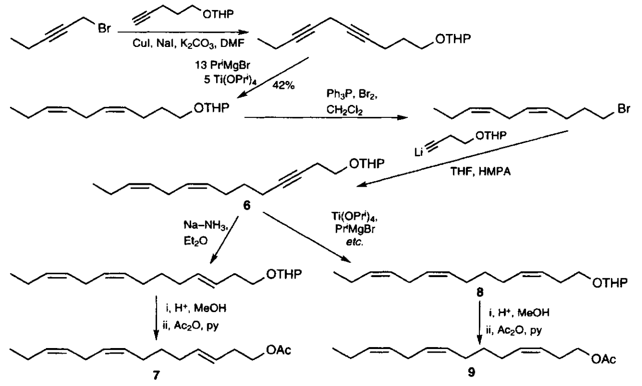
The range of reductions achieved is shown in Table 1; conjugated diynes are reduced to the corresponding *Z*-dienes and skipped enynes are reduced to skipped dienes without difficulty (entry 5). The yields of isolated, pure products are moderate and in some cases are lowered by the instability of the poly-yne starting materials, which must be utilised immediately after preparation.

For access to **1**, the tetrahydropyran-2′-yl ether of octadeca-9,12,15-triyn-1-ol **2** was treated with Ti(OPr^i)$_4$ (8 equiv.) and Pr^{i}MgBr (20 equiv.) and then quenched with D_2O to afford **1**.† Presumably, a methylene skipped tris(titanacylopropene) intermediate[6,7] is involved, as shown in Scheme 3.

The GC–MS, ^{1}H and ^{13}C NMR spectra indicated a very high level of ^{2}H incorporation, and analysis of the vinylic region of the ^{13}C spectrum (δ 126–132) was possible on the basis of a single hexadeuterio species, with a low level of residual protium.[8]

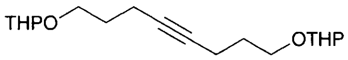
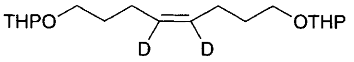
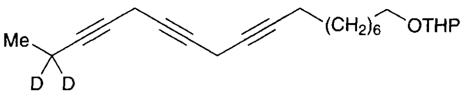
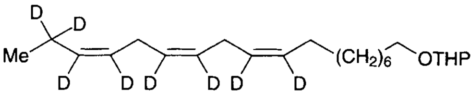
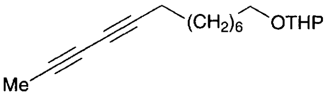
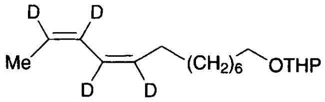
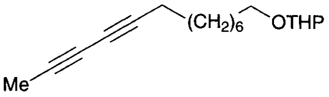
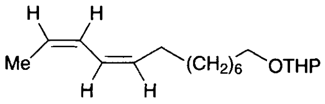
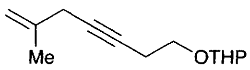
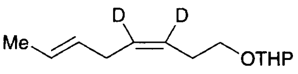
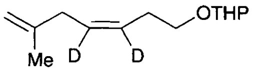


Scheme 3



Scheme 4

Table 1 Ti^{II}-mediated reduction of alkynes to *Z*-alkenes

Entry	Starting alkyne[a]	Reagents[b] $\left[\frac{Pr^iMgBr}{Ti(OPr^i)_4}\right]$	Product[a,c]	Isolated yield[d] (%)
1		5 : 2		81 (crude)
2		20 : 8		33
3		11 : 4		46
4		13 : 5		41[e]
5	 	13 : 5	 	70 (crude)

[a] Starting materials and products were characterised by high resolution mass spectra, GC–MS and ^1H and ^{13}C NMR spectra. ^2H NMR spectra were obtained for deuteriated products. [b] Per mole of starting alkynyl compound. [c] Deuterium-containing *Z*-alkenes were obtained by quenching with *ca.* 99.5% D_2O; others from use of H_2O. [d] After flash chromatography. [e] This yield was increased to 55–60%, (after chromatography) by quenching with H_2O–NH_4Cl or 10% aqueous HCl. Reagent ratio of 6.2 : 2.5 was used in these experiments.

The finding that skipped diynes are readily reduced to skipped *Z,Z*-dienes without detectable isomerisation suggested application to the synthesis of natural systems incorporating such an arrangement. A recent example is (3*E*,8*Z*,11*Z*)-tetradeca-3,8,11-trien-1-yl acetate **7**, the major sex-attractant of *Scrobipalpuloides absoluta*, a pest of tomatoes.[9] The approach is shown in Scheme 4 with a key step being Ti^{II}-mediated reduction to a skipped diene followed by coupling with the appropriate alkyne. Reaction of the alkyne **6** with Na–NH_3 provides **7**,‡ whereas the all-*Z* configured isomer **9**, was obtained by Ti^{II}-mediated reduction§ of **6**.

The present method is attractive as (i) it employs cheap and commercially available materials [$Ti(OPr^i)_4$, Pr^iMgBr] and an inexpensive source of deuterium (D_2O), should labelling be required (tritium labelling would also be possible); (ii) the conversion appears to be regio- and stereo-specific, affording pure *Z*-configured alkenes, and no scrambling when ^2H-labelling is conducted; (iii) the method is operationally simple, and under- or over-reduction is negligible when the appropriate stoichiometry of reagents is employed; (iv) other electrophiles, particularly organometal halides (*e.g.* of Sn) could be employed to give *Z*-configured stannanes for coupling chemistry. This feature is currently being explored.

Footnotes

† The preparation of **1** is given as a typical procedure: $Ti(OPr^i)_4$ (1.343 g, 4.73 mmol) and starting alkyne **2** (0.202 g, 0.591 mmol) were dissolved in dry ether (15 ml), under N_2, and cooled to −70 °C. Pr^iMgBr (9.45 ml, 11.81 mmol, *ca.* 1.25 mol l^{-1} solution in dry ether) was added dropwise *via* cannula. The reaction mixture was then warmed to −30 °C for 2 h, during which time a dark brown colour formed. Upon cooling to −70 °C, D_2O or H_2O (0.5 ml) was added, and the mixture allowed to warm to room temp. After filtration through super-cel and washing with ether, the filtrate was dried ($MgSO_4$) and evaporated to yield an oil. Flash chromatography (1 : 20, ether–hexane) provided pure **1**, (52 mg, 25%).

‡ Our ^1H, ^{13}C NMR and EI mass spectra for **7** matched those obtained by Dr A. Attygalle and Professor J. Meinwald of Cornell University. We are grateful to them for conducting the comparisons.

§ In the reduction of **6** to yield **8**, two other isomers of **8** were significant components. All three were converted to their corresponding acetates (M = 250) and the required **9** was obtained pure by chromatography on SiO_2–$AgNO_3$. The minor components appeared to be isomers of **9**, but are not methylene skipped dienes (from ^1H NMR), and we presume isomerisation of the *Z,Z*-methylene skipped diene system. However, other results show that the appropriate triyne [1-(tetrahydropyran-2′-yloxy)tetradeca-3,8,11-triyne] would be cleanly reduced to the all-*Z*-arrangement.

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8 This ^{13}C spectrum exhibits signal broadening and upfield shifting associated with the presence of the deuterium atoms. For some examples and leading references, see K. G. Penman, W. Kitching and A. P. Wells, *J. Chem. Soc., Perkin Trans. 1*, 1991, 721. The spectra of related systems are presented in ref. 3.

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