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A Stereoselective Synthesis of Conjugated Trans Trienes: Low-Valent Titanium Induced Reductive Elimination of 1,6-Dibenzoate-2,4-dienes

Guy Solladie*, Guy B. Stone, Almudena Rubio,[1]

Ecole Européenne des Hautes Etudes des Industries Chimiques (EHICS) Laboratoire de
Stéréochimie associé au CNRS, 1, rue Blaise Pascal, F-67008 Strasbourg, France

Abstract: A stereoselective synthesis of all-trans trienes is described via low valent titanium reductive elimination of 1,6-dibenzoate-2,4-dienes.

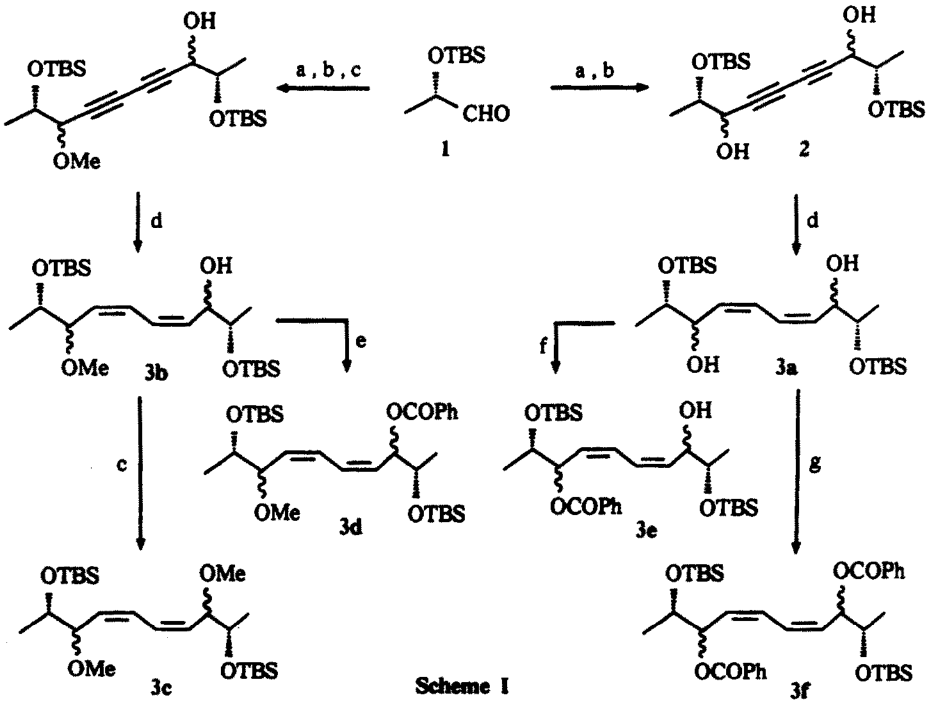
Conjugated polyolefinic fragments are found in a wide variety of interesting and important organic compounds. Several examples of natural products include: the polyene macrolides[2a] (over 200 members reported to date) which display potent antiviral activity and have been successfully employed in antifungal therapy; carotenoids[2b] that act as pigments in nature; leukotrienes[2c] which are known to mediate immediate hypersensitivity reactions and inflammation. Uses of such systems as energy transfer reagents in photochemical reactions have also been reported[2d]. In light of these and other examples, the efficient assembly of conjugated polyolefinic chains is desireable. In our continuing studies in the area of polyene synthesis, we wish to report now our discovery of a stereoselective method for the formation of conjugated trans-trienes via a low-valent titanium induced reductive elimination of 1,6-dibenzoate-2,4-dienes.

Walborsky[3] was the first to report that 1,3-dienes could be prepared by the low-valent titanium reductive elimination of 2-ene-1,4-diols and we have since applied this method to the synthesis of several natural products and analogues[4]. Following these results, we began a study of the formation of trienes[5] by the same type of elimination starting from 1,6-diol-2,4-dienes.

The diene-diol system **3a** was prepared (Scheme I) via stepwise condensation of diacetylene[6] with the aldehyde **1** derived from (+)(R). methyl lactate, followed by stereospecific cis reduction of the diyne using an activated zinc-copper couple[7]. The compound **3a**, with a pure cis-cis geometry in the dienic moiety (coupling constants of 11.6 Hz were measured for the vinylic protons), was isolated as a mixture of 3 diastereomers which could easily be separated by column chromatography (**A** , least polar isomer; **B** minor isomer; **C** major and most polar isomer).

Ti(0) reductive elimination was then applied, under the usual conditions[4,8], to each diastereomer of compound **3a**. In sharp contrast with our previous studies on vitamin A analogues, yields were very low and curiously only the more polar and major diastereomer **C** gave the all-trans triene **I**[9]. The other diastereomers (**A**,**B**) yielded only a geometric mixture of triene isomers (Table I).

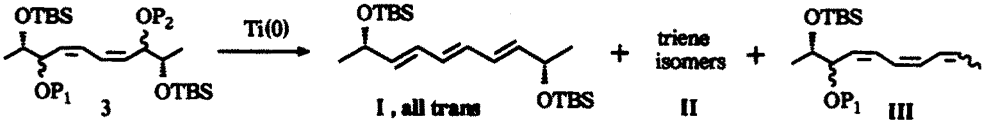
During our studies of diene formation via titanium reductive elimination of 2-ene-1,4-diols, it had been observed[10] that protection of the alcohols had in some cases influenced the stereochemical outcome as well improved the yield. This approach was applied to the 1,6-diol-2,4-diene system and thus we prepared compounds **3b**-**3f**. The results listed in Table I show that the stereoselectivity of the reaction was dramatically improved by protecting both OH groups (**3c**, **3d**, **3f**) and in the case of the dibenzoate **3f** we observed only the exclusive formation, in almost quantitative yields[11], of the



Scheme I

a) H—≡—≡—MgBr , 0°C, 75%; b). EtMgBr, then 1, - 78°C, 78%; c).NaH, MeI, THF, 0°C to r.t., 80% ; d). Zn/Cu, MeOH-H_2O, r.t., 80%; e). PhCOCl (1 eq.), pyridine, 90%; f). PhCOCl (1 eq.), pyridine, r.t., 58%; g). PhCOCl (2 eq.), pyridine, r.t., 71%.

Table I. Low valent titanium reductive elimination of 3.

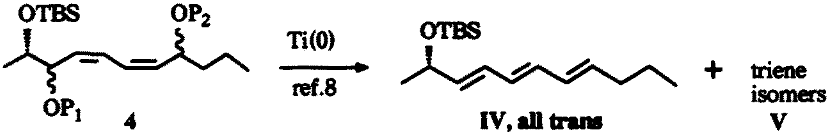


3	P_1	P_2	Dia.	yield%	I	II	III
3a	H	H	A	19	0	1	0
			C	16	1	0	0
3b	Me	H	A	34	0	1	1
			B	32	0	1	1
			C	36	1	0	1
3c	Me	Me	C	40	1	0	1
3d	Me	COPh	A	28	1	0	0
			B	23	1	0	0
			C	33	1	0	0
3e	COPh	H	A	59	8	0	1
3f	COPh	COPh	A	97	1	0	0
			B	90	1	0	0
			C	94	1	0	0

all-trans triene I regardless of the starting diastereomer. A side product III, resulting from a vicinal diol elimination, was observed in cases where a free OH group was present[12].

Table II reports another example confirming the preceeding results. The diene-diol 4 was made in a similar way from aldehyde 1, diacetylene and butanal, followed by reduction of the triple bonds with Zn-Cu. The two major diastereomers (A more polar, B less polar) were separated and subjected to Ti(0) studies (Table II). The two diastereomers A and B of compounds 4a and 4b showed different behavior upon exposure to the Ti(0) reaction: only the more polar isomer B gave the all-trans triene[13] in a moderate yield, whereas both dibenzoate diastereomers 4c gave only the all-trans triene in high yield regardless of the diol configuration.

Table II. Low valent titanium reductive elimination of 4.



4	P^1	P^2	Dia.	Yield %	IV	V
4a	H	H	A B	43 43	0 1	1 0
4b	Me	H	A B	55 76	0 1	1 0
4c	COPh	COPh	A B	86 88	1 1	0 0

Hence, low-valent titanium reductive elimination of 1,6-dibenzoate-2,4-dienes, readily obtained in 2 steps from the corresponding 1,6-diol-2,4-diyne, is a highly stereoselective and a high yielding reaction allowing the synthesis of pure all-trans trienes. Application of this method in the total synthesis of 6(E), 5(S), 12(R) leukotriene B_4 is reported in the following communication.

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REFERENCES AND NOTES

1. On leave from the Universidad Autonoma, Madrid (Spain)

2. (a) Progress in the Chemistry of Organic Natural Products, Ed. L. Zechmeister, Wien Springer Verlag 1963, Vienna, vol. 21, P. 17; *ibid* Ed. W. Herz, New York, 1977, vol. 30, P. 360; (b) Eugster, E. H.; Marki-Fischer, E. *Angew. Chem. Int. Edit.*, **1991**, *30*, 654; (c) Ford-Hutchinson, A.; Bray, M. A.; Doig, M. V. Shipley, M. E.; Smith, M. J. H., *Nature* **1980**, *286*, 264; (d) Samuelson, B. *Science*, **1990**, *220*, 568; (e) Lehn, J. M. *Angew. Chem. Int. Ed.*, **1990**, *29*, 1304.

3. Walborsky, H. M.; Wust, H. H.; *J. Am. Chem. Soc.* **1982**, *104*, 5807.

4. (a) Solladié, G.; Hutt, J.; *J. Org. Chem.* **1987**, *52*, 3560-3566; (b) Solladié, G., Girardin, A., *Tetrahedron Lett.* **1988**, *29*, 213; (c) Solladié, G.; Girardin, A.; Lang, G., *J. Org. Chem.* **1989**, *54*, 2620-2628.; (d) Solladié, G.; Berl, V., *Tetrahedron Lett.* **1992**, *33*, 3477-80.

5. In a personal communication, Professor Walborsky suggested that the same type of elimination might be possible for the formation of trienes.
6. Brandsma, L., *Preparative Acetylenic Chemistry*, Elsevier **1971**, p. 122.

7. Boland, W.; Schröder, N.; Sieler, C.; Feigel, N., *Helv. Chim. Acta.* **1987**, *70*, 1025.

8. Ti(0) was prepared by reduction of $TiCl_3$ (2 eq) by $LiAlH_4$ (1 eq) in THF. The diene-diol in THF was added to the Ti(0) suspension (usually 2.5 eq) and then the reaction flask was placed in an oil bath already at 65-70°C. After completion (usually about 1.5 h), the reaction was quenched at 0 °C (H_2O,then 1% HCl) followed by ether extraction. Determination of % trans was determined by ^1H NMR of the crude product (purification by column chromatography).

9. The all-trans stereochemistry was assigned from the ^1H NMR spectrum of I and of the mono-deprotected product (2S, 9S)-2-*t*-butyldimethylsiloxy-9-hydroxy-3,5,7-decatriene (obtained from I with one equivalent of TBAF in THF followed by purification by chromatography). The trans coupling constant $J_{3-4} = J_{7-8} = 14.5$ Hz could be determined from both spectra in d_6 benzene. The $J_{5-6} = 14.6$ Hz was determined on the molecule having a free OH and in the presence of a stoichiometric amount of $Pr(FOD)_3$ in d_6 benzene.

10. Solladié, G.; Andres, J. M.; Stone, G. B.; Berl, V., results to be published..

11. The dibenzoate (3f,4c), in dry THF (0.09 M) was added to a suspension of Ti(0) (4-6 equiv, 0.2 M in THF) at 65 °C under Argon for 0.5 - 2h. The reaction can be applied to the mixture of diastereomers. The reaction is very rapid at 65 °C (30 min) with no sign of side products.

12. The structure III was easily identified by ^1H NMR from the absence of one TBDMS group and the presence of 6 vinylic protons.

13. The all-trans configuration of compound IV was determined by the same method used for compound I: deprotection of alcohol and ^1H NMR studies using $Pr(FOD)_3$ in d_6 benzene.

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