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Tetrahedron Letters 49 (2008) 1169–1174
Tetrahedron Letters

Stereoselective synthesis of chiral tertiary alcohol building blocks via neighbouring group participation from tri-substituted olefins

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Received 9 November 2007; revised 4 December 2007; accepted 10 December 2007
Available online 15 December 2007

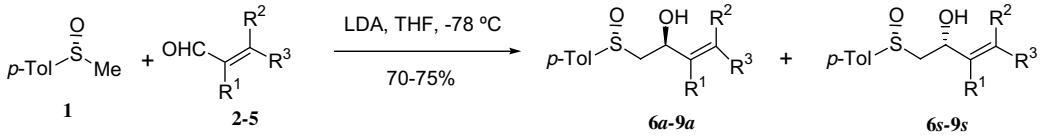
Abstract

A regio- and stereoselective preparation of chiral quaternary 1,2/1,3-diols from acyclic tri-substituted alkenes is disclosed. Optically active tertiary alcohols are the constituents of several bioactive natural products, pharmaceuticals and a general method for their preparation is desirable. A sulfinyl moiety has been utilized as an intramolecular nucleophile.

Keywords: Chiral quaternary 1,2/1,3-diols; Tri-substituted alkenes; Sulfoxide

The introduction of a chiral quaternary carbon centre poses a considerable challenge to synthetic organic chemists.[1] Optically active tertiary alcohols are the constituents of several bioactive natural products,[2] pharmaceuticals and employed as versatile building blocks. Much effort has therefore been devoted to the synthesis of chiral tertiary alcohols, these include (a) asymmetric oxidation[3] (b) desymmetrization of prochiral tertiary alcohols[4] (c) enantio-/diastereoselective nucleophilic addition to ketones[5] and (d) stereospecific insertion of carbene into secondary alcohols.[6] Since most of the reported methods have their limitation in terms of the substrate diversity, new methods applicable to a variety of substrates are needed. In this context, we report herein, a highly regio- and stereoselective preparation of chiral 1,2/1,3 diols possessing a quaternary stereogenic centre from acyclic tri-substituted allyl alcohols.[7] We also present the utility of one of the building blocks for the synthesis of C7–C11 fragment of fostriecin.

The olefinic substrates **6**–**9** were prepared as an equimolar mixture of epimers by condensing the lithium anion of methyl *p*-tolyl sulfoxide[8] **1** and unsaturated aldehydes[9] **2**–**5**, Scheme 1. The *anti*-(**6*a***–**9*a***) and *syn*-isomers[10] (**6*s***–**9*s***) were



2, **6**; R^1 = H, R^2 = CH_2OPMB, R^3 = Me
3, **7**; R^1 = H, R^2 = Me, R^3 = CH_2OPMB
4, **8**; R^1 = Me, R^2 = CH_2OBPS, R^3 = H
5, **9**; R^1 = Me, R^2 = H, R^3 = CH_2OBPS

Scheme 1.

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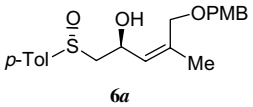
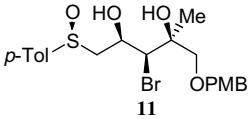
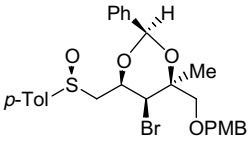
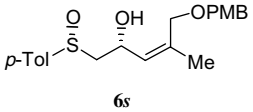
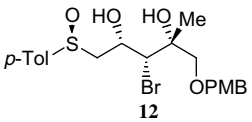
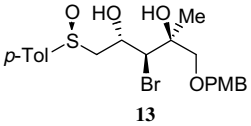
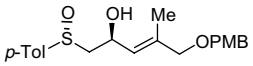
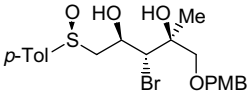
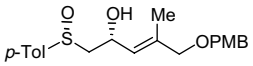
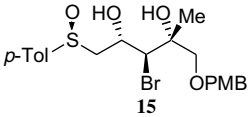
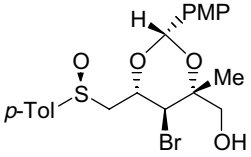
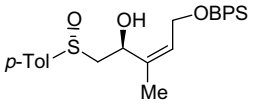
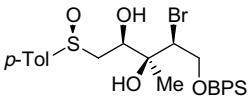
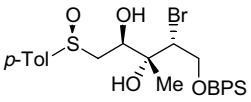
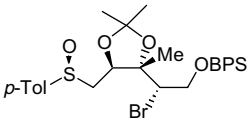
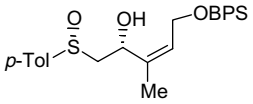
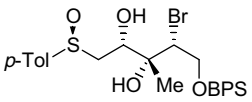
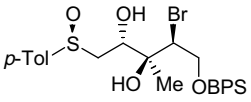
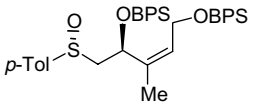
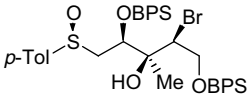
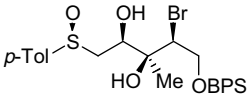
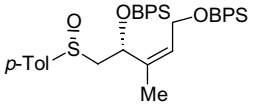
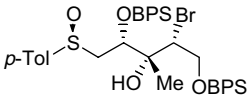
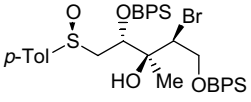
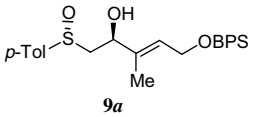
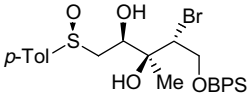
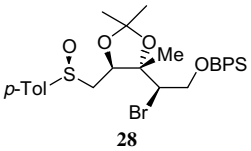
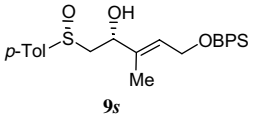
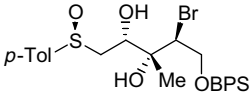
doi:10.1016/j.tetlet.2007.12.046

Table 1
Regio- and stereoselective chiral tertiary alcohol preparation[a]

S. No	Substrate	Product		Yield % (*Syn*:*Anti*)	Derivative
		Syn C2,C3	*Anti* C2,C3		
1	 **6*a***	 **11**		80 (>95:<5)[b]	 **25**
2	 **6*s***	 **12**	 **13**	78 (1:2)[c]	
3	 **7*a***		 **14**	78 (<5:>95)[b]	
4	 **7*s***		 **15**	76 (<5:>95)[b]	 **26**
5	 **8*a***	 **16**	 **17**	80 (1:1)	 **27**
6	 **8*s***	 **18**	 **19**	79 (2:1)[c]	
7	 **10*a***	 **20**		81 (>95:<5)[b]	 **16**
8	 **10*s***	 **21**	 **22**	82 (3:1)[c]	
9	 **9*a***	 **23**		82 (>95:<5)[b]	 **28**
10	 **9*s***	 **24**		80 (>95:<5)[b]	

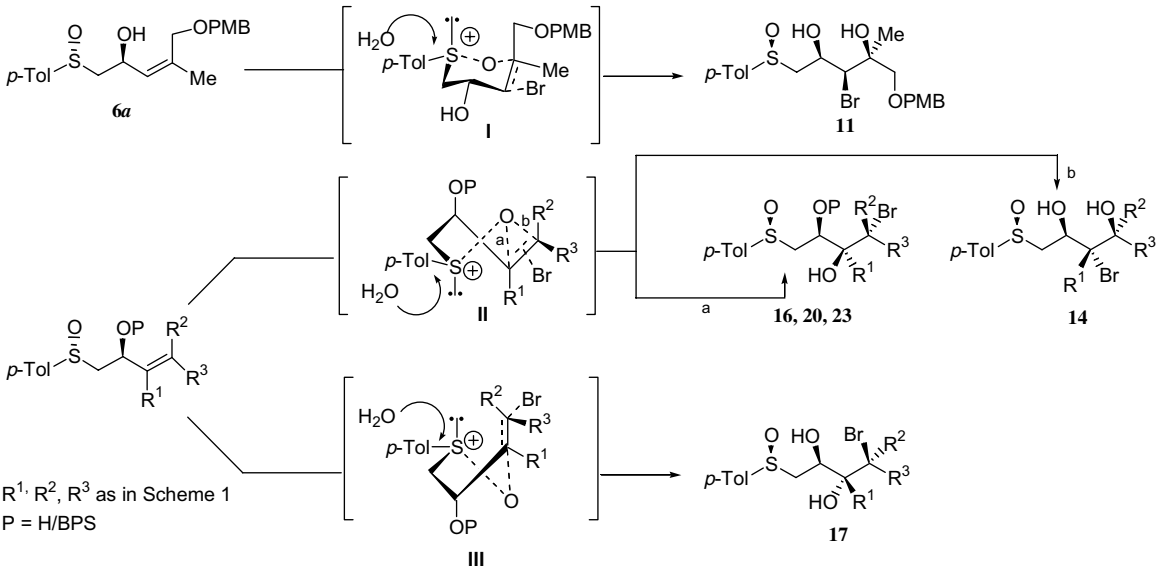
[a] All reactions were carried out on a 0.5 mmol scale using 1.2 equiv of NBS, 1.5 equiv of H_2O in toluene as solvent (0.2 M).
[b] Crude product NMR did not reveal peaks for other isomers.
[c] The isomers were inseparable by column chromatography.

separated and subjected to a reaction with freshly recrystallized *N*-bromosuccinimide (NBS) in toluene in the presence of water to afford tertiary alcohols (Table 1) regio- and stereoselectively in good yield.

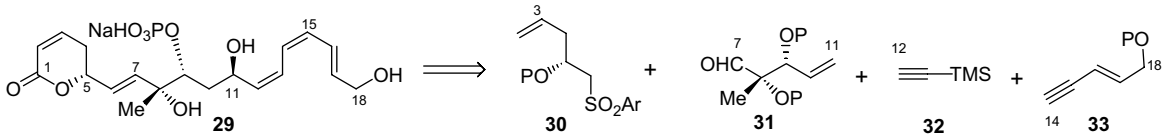
A perusal of the table reveals that the reaction is general, high yielding and obeys Markonikov's rule[11] to afford products regiospecifically, wherein the nucleophile is linked to the more substituted carbon or the most electrophilic centre.[12] The structures were assigned by NMR (and NOE) study on the acetonides[13] derived from diols **11**, **15**, **16** and **23**. Deprotection of the silyl groups in **20** followed by selective reprotection of the primary hydroxy group yielded **16**, thereby confirming the structure assigned to **20**. The enantiomeric relationship at C2–C4 between **14** and **15** was apparent after individually oxidizing them to the corresponding sulfones, whose ^{1}H NMR were identical. A similar oxidation proved the enantiomeric relationships at carbon atoms of **11/12**, **16/18** and **23/24**. The regio- and stereochemical outcome[14] (illustrated only for *anti* series) of the reaction in entry 1 can be rationalized by invoking intermediate **I**, resulting from the rate-determining nucleophilic attack by the sulfinyl moiety onto a Π-complexed bromonium ion, wherein A(1,3) interactions are minimized. Intermediate **II**, arising similarly would account for the only product in entries 3,7,9 and product **16** in entry 5. Product **17** in entry 5 could be arising via intermediate **III**. The strong destabilizing A(1,2) steric interactions that would be encountered between the siloxy and the methyl (R^1) substituent in **III** would account for the exclusive formation of **20** from **10a** via **II** (entry 7), Scheme 2.

The relative stereochemistry at sulfur and carbon atoms influences the stereoselectivity (compare entries 1/2, 5/6 and 7/8). By an appropriate choice of the *anti*/*syn*-isomers (compare entries 1/2 and 7/8) or by suitably protecting the allylic hydroxyl group (compare entries 5/7), the stereoselectivity can be improved so as to get one isomer exclusively. *Syn* 1,2- and 1,3-diols with a quaternary stereogenic centre are thus readily obtained regio- and stereoselectively. It is worthwhile to note that by the reduction of the β-ketosulfoxide, obtained for instance, by reacting the lithium anion of methyl *p*-tolylsulfoxide with the esters corresponding to **2–5,** with DIBAL-H or DIBAL-H/$ZnCl_2$,[15] the *anti*- or *syn*-isomers, respectively, can be obtained diastereoselectively. The presence of functional groups like bromine, sulfoxide and hydroxy groups provides a wide scope for manipulations, further carbon–carbon and carbon–heteroatom bond formations by intermolecular reactions. Also the bromohydrins can be readily transformed into chiral epoxides which are important intermediates,[16] using either the secondary or tertiary hydroxy group. Also the hydroxymethyl and sulfinyl groups provide suitable handles for further elaboration at either ends of the molecule. As an illustration of the utility of the methodology we describe the synthesis of the C7–C11 fragment **31**, of fostriecin,[17] Scheme 3. It was envisaged to construct (i) the C6–C7 double bond by a Julia olefination[18] between subunits **30** and **31** and (ii) the lactone ring via a RCM reaction. In the resulting product, an aldehyde group at C11 was envisioned to be introduced by a selective hydroboration followed by oxidation. Further, the 1,3-asymmetric induction due to C9 substituent was to be capitalized on for introducing the C11 stereocentre selectively while forming the C11–C12 bond using **32**. Cadiotz–Chodkiewicz coupling[19] using enyne **33** and further routine transformations were expected to furnish fostriecin. Compound **31** was envisioned to be derived from 1,3-diol **15**.

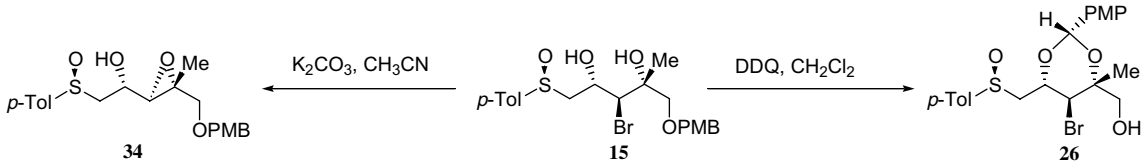
Epoxide formation by the selective participation of the secondary hydroxy group in **15** followed by the reductive elimination of sulfinyl moiety was expected to furnish the required allyl alcohol. In the event, the treatment of **15**[20]



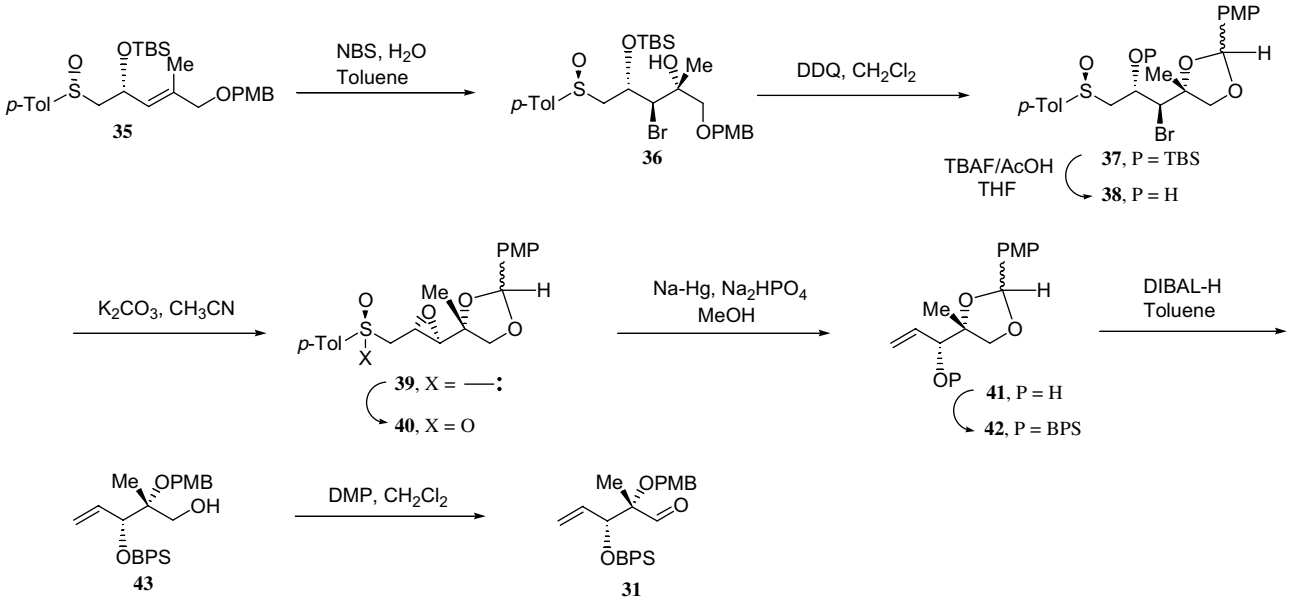
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

with anhydrous potassium carbonate in acetonitrile afforded epoxide **34** (89% yield) as the only product. The tertiary hydroxyl group therefore needed to be protected. Treatment of **15** with DDQ[21] did not afford the 1,2-acetonide but the rearranged 1,3-acetonide **26** (76% yield) as the only product, Scheme 4.

Silyl ether **35** (90% yield) derived from **7s** was reacted with NBS to furnish bromohydrin **36** (76% yield, 9:1 dr, minor isomer not depicted). 1,2-Acetonide formation with DDQ proceeded without an incident to yield **37** as an epimeric mixture (75% yield). Deprotection of the silyl group using buffered TBAF and epoxide formation by base treatment yielded **39** (81% for two steps). Reductive elimination[22] of epoxy sulfoxide proceeded less cleanly in comparison to the corresponding sulfone **40** to yield allyl alcohol **41** (64% overall yield), which was protected as its silyl ether **42** (92% yield). Regioselective reduction of the acetonide with DIBAL-H furnished primary alcohol **43** as a 9:1 mixture of regioisomers (76% yield). Oxidation of **43** with DMP[23] proceeded cleanly to yield aldehyde **31** (95% yield), Scheme 5.

In conclusion, we have disclosed a highly regio- and stereoselective method for the preparation of 1,2- and 1,3-diols possessing a quaternary chiral centre. The methodology is general, high yielding and affords building blocks useful for the natural products synthesis. The synthesis of few natural products is presently underway and these would form subjects for later communications from our laboratory.

Acknowledgements

S.R. is thankful to Dr. J. M. Rao, Head, Org. Div. I and Dr. J. S. Yadav, Director, I.I.C.T, for constant support and encouragement. T.S is thankful to CSIR, New Delhi for a fellowship. Financial assistance from DST (New

Delhi) is gratefully acknowledged. We thank Dr. A. C. Kunwar for the NMR spectra and Dr. M. Vairamani for the mass spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.046.

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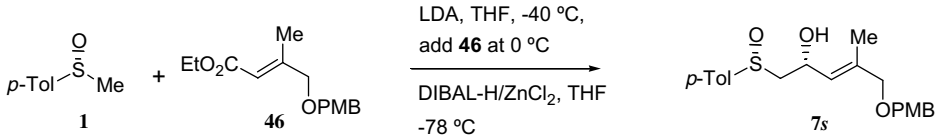
20. Compound **15** was obtained from **7*s*** prepared in two steps (i. formation of β-keto sulfoxide and ii. stereoselective reduction of keto sulfoxide, 53% overall yield) as depicted.



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