JOC Article

Stereoselective Anti Aldol Reactions of Erythrulose Derivatives. Functionalized Chiral d^3 and d^4 Synthons

Juan Murga,[†] Purificación Ruiz,[†] Eva Falomir,[†] Miguel Carda,*[,†] Gabriel Peris,[‡] and J. Alberto Marco*[,§]

Departamento de Química Inorgánica y Orgánica, and Servicios Centrales de Instrumentación, Universidad Jaume I, E-12080 Castellón, and Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain

alberto.marco@uv.es

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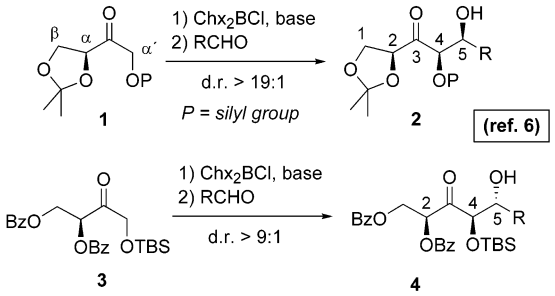
An improved procedure for the synthesis of anti aldols from protected erythrulose derivatives is reported. The preparation of functionalized d^3 and d^4 synthons with various stereochemical arrays by means of this methodology is described and subsequently applied to a stereoselective formal synthesis of the natural metabolite goniothalesdiol.

Introduction

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon−carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] Our current interest in the development of erythrulose[3] as a useful chiral C_4 building block for the stereocontrolled construction of polyfunctionalized structures has prompted us to investigate the enolization of protected derivatives thereof and the subsequent addition of the resulting enolates to aldehydes. We have reported that L-erythrulose acetals of the general formula **1** (Scheme 1, protecting group P = triethylsilyl, TES; *tert*-butyldimethylsilyl, TBS; or *tert*-butyldiphenylsilyl, TPS), readily prepared in two steps from L-erythrulose,[4] can be transformed into boron enolates provided that chlorodicyclohexylborane (Chx_2BCl) is used as the enolization reagent.[5] These boron enolates were then allowed to react with a range of achiral aldehydes to yield aldol adducts of the general formula **2** with a high degree of syn 1,2- and 1,3-induction (i.e., the 2,4-syn/4,5-syn relationship in **2**).[6]

SCHEME 1. Aldol Reactions of Erythrulose Derivatives 1 and 3 (TBS = *tert*-Butyldimethylsilyl; dr = Diastereomeric Ratio)



Prior to our research, only one case of a syn aldol addition mediated by this reagent had been reported. Paterson and co-workers described the use of an ethyl ketone bearing an α-benzyloxy group, where a syn aldol was formed with good diastereoselectivity.[7] The authors related this unanticipated syn bias to the formation of a *Z* enolate instead of the expected *E* isomer, a feature

[†] Departamento de Química Inorgánica y Orgánica, Universidad Jaume I.

[‡] Servicios Centrales de Instrumentación, Universidad Jaume I.

[§] Departamento de Química Orgánica, Universidad de Valencia.

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203−331. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 111−212. (e) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99−111. (f) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2. (g) Mekelburger, H. B.; Wilcox, C. S. In ref 1f, pp 99−131. (h) Heathcock, C. H. In ref 1f, pp 133−179 and 181−238. (i) Kim, B. M.; Williams, S. F.; Masamune, S. In ref 1f, pp 239−275. (j) Rathke, M. W.; Weipert, P. In ref 1f, pp 277−299. (k) Paterson, I. In ref 1f, pp 301−319. (l) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317−338. (m) Braun, M. In *Houben-Weyl's Methods of Organic Chemistry, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1603−1666 and 1713−1735. (n) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120.

(2) (a) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (b) Tatsuta, K. In ref 2a, pp 1−38. (c) Blizzard, T., Fisher, M., Mrozik, H.; Shih, T. In ref 2a, pp 65−102. (d) Isobe, M. In ref 2a, pp 103−134. (e) Beau, J.-M. In ref 2a, pp 135−182. (f) Yonemitsu, O.; Horita, K. In ref 2a, pp 447−466. (g) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114.

(3) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, M. *J. Org. Chem.* **1998**, *63*, 698−707 and references therein.

(4) (a) For an improved preparation of silylated L-erythrulose acetonides **1** (P = TES, TBS, TPS) from L-erythrulose hydrate, see: Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999**, *29*, 2601−2610. (b) For the preparation of protected D- and L-erythrulose derivatives using chiral precursors other than erythrulose itself, see: Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996**, 1801−1810.

(5) For a general review of boron aldol reactions, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

(6) Murga, J.; Falomir, E.; González, F.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 9697−9707. Aldol reactions of ketone **1** with chiral aldehydes have also been investigated: Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577−8582.

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attributed in turn to the deprotonation step taking place in a chelate involving the boron, carbonyl oxygen, and α-oxygen atoms.[8] They further reasoned that replacement of the benzyl by the electron-attracting benzoyl group would make the α-oxygen atom more electron-poor and thus prevent the formation of such a chelate, with subsequent reversal of the stereochemical course to the expected anti aldol formation via an *E* enolate. Their conclusions were then borne out by experimental results.[7a,b] In view of this, we first checked whether a *Z* boron enolate was being formed when ketone **1** was treated with Chx_2BCl. That was found indeed to be the case.[6] Then, we checked whether the introduction of electron-withdrawing protective groups in **1** would change the stereochemical course of the reaction. As a matter of fact, it was found that, in line with Paterson's reasonings, aldol reactions with ketone **3**, which bears two benzoyl protecting groups, give rise stereoselectively to anti aldols **4** (relative configuration at C_4-C_5), most likely through the corresponding *E* boron enolate. Quantum-mechanical studies provided a theoretical basis for these results.[6]

These results are interesting from a synthetic point of view, as the resulting aldols can be used for the synthesis of various polyoxygenated molecules, even very complex ones.[9,10] However, ketone **3** has one drawback: its synthesis requires eight steps from L-ascorbic acid.[6] It would be much more practical if it could be prepared from L-erythrulose itself in fewer steps. However, the two primary hydroxyl groups of this ketotetrose cannot be efficiently differentiated from one another, this differentiation being necessary if an orthogonality of the protecting groups of the aldols is subsequently required.[11] Since the key to having anti aldols seems to rely on the presence of an α-acyloxy group, we wondered whether a ketone with general structure **5** (Scheme 2, R = acyl group) would behave in the same way as **3**. Ketones **5**, available from L-erythrulose, have two identical *tert*-butyldimethylsilyl (TBS) groups at the primary hydroxyl functions[12] but, since one of them becomes secondary in the final aldol, selective deprotection should be feasible. Furthermore, the secondary hydroxyl group is acylated and therefore equally amenable to selective cleavage. The preparation of ketones **5**, the investigation of their behavior in aldol reactions, and the synthesis of polyoxygenated d^3 and d^4 synthons therefrom constitute the main contents of the present manuscript. In addition, a formal, stereoselective synthesis of the natural metabolite goniothalesdiol is described as a practical application of this methodology.

SCHEME 2. Aldol Reactions of Erythrulose Derivatives 5a−c

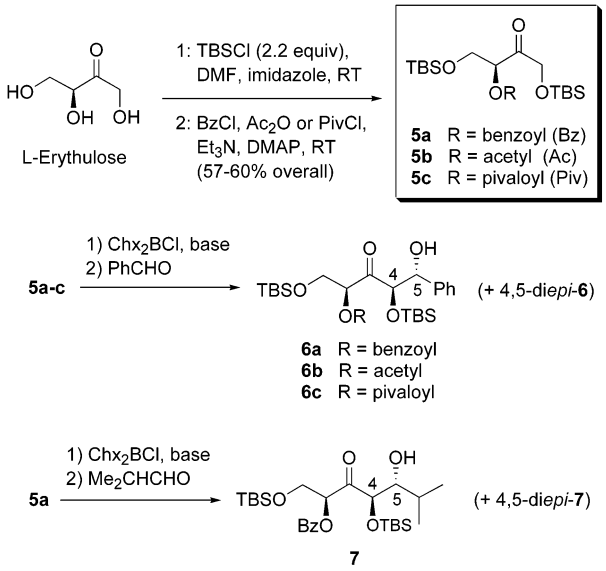


TABLE 1. Yields and Diastereomeric Ratios in Aldol Reactions of Ketones 5a−c

ketone	aldehyde	yield[a] (%)	dr[b]
5a	PhCHO	86	92:8
5b	PhCHO	77	90:10
5c	PhCHO	82	92:8
5a	Me_2CHCHO	87	85:15

[a] Overall yield of the diastereomeric mixture. [b] dr determined by means of ^1H and ^{13}C NMR.

Results and Discussion

Ketones **5a−c** bearing three different acyl groups, which basically differred in their size, were readily prepared from L-erythrulose in only two steps (Scheme 2). The aldol reactions of these three ketones with benzaldehyde were first investigated. Gratifyingly, anti aldols **6a−c** were formed with good stereoselectivity, similar to that observed with ketone **3**.[13] As seen in Table 1, the size of the acyl group does not play a decisive role in the outcome of the process. However, yields and diastereoselectivities were slightly higher with the benzoylated derivative **5a**. Since the benzoyl group additionally provided UV-fluorescence in TLC plates, only ketone

(7) (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083−9086. (b) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652. After our results, a further example of preparation of *syn* aldols using Chx_2BCl appeared in the literature: Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2000**, *2*, 2599−2602.

(8) Recent experimental findings of our group indicate that formation of *syn* aldols from α-oxygenated ketones may occur even in cases where the formation of chelates is unlikely: Murga, J.; Falomir, E.; Carda, M.; González, F.; Marco, J. A. *Org. Lett.* **2001**, *3*, 901−904.

(9) (a) Falomir, E. Ph.D. Thesis, University of Castellón, Spain, 1998. (b) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677−683.

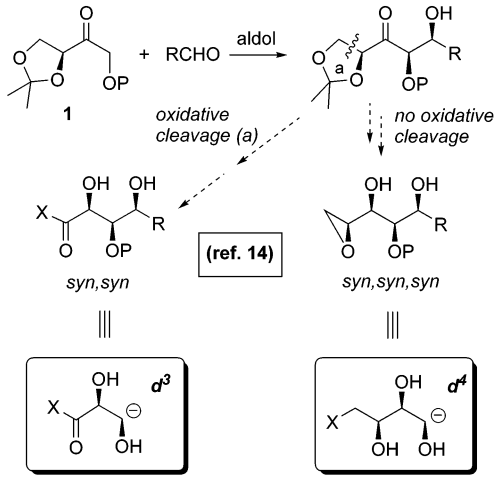
(10) Forsyth and co-workers have recently used ketone **3** in their synthetic approach to azaspiracid: Forsyth, C. J.; Hao, J.; Aiguadé, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3663−3667.

(11) For this reason, tri-*O*-benzoyl-L-erythrulose was not considered for the purposes described here.

(12) Ketones **5** with triethylsilyl groups were not obtained in good yield, due to the formation of appreciable amounts of trisilylated erythrulose in the silylation step. Furthermore, ketones **5** bearing *tert*-butyldiphenylsilyl groups were found less reactive and less diastereoselective as well. Thus, only ketones **5** with *tert*-butyldimethylsilyl groups are discussed here.

(13) The configurations of the major aldols and of its reduction products were established with the aid of chemical correlations described in the Supporting Information. In the case of aldol **6a**, further comformation was provided by the conversion into goniothalesdiol precursor **23** (see Scheme 6). The configuration of aldol **7** was secured by means of an X-ray diffraction analysis. Crystallographic data of this compound (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supporting Information with reference CCDC-223372. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223−336033 or e-mail: deposit@ccdc.cam.ac.uk]. The minor aldols were found to be also anti according to NMR examination of the aldol mixture (diagnostic value of $J_{4,5} \sim 5-7$ Hz for anti aldols but ≤ 2 Hz for syn aldols). The isolation of these minor aldols, however, was not attempted.

SCHEME 3. Functionalized d^3 and d^4 Chiral Synthons Generated from Syn Aldols of Erythrulose Derivatives

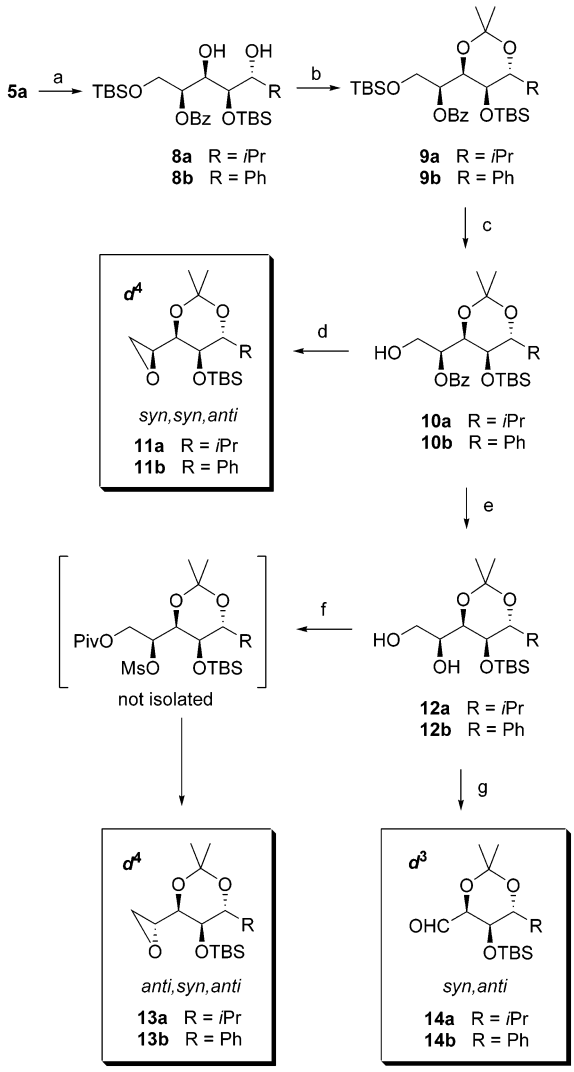


5a was used in subsequent work. Aldol reaction of the latter with isobutyraldehyde gave aldol **7** with dr 85:15.[13] While the aldol process was in this case somewhat less diastereoselective than with ketone **3**, this was amply compensated by the much shorter route to **5a**.

After having established the feasibility of anti aldol reactions with ketone **5a**, we set out to develop practical applications for this synthetic methodology. In a previous communication of our group, we showed that polyfunctionalized d^3 and d^4 synthons (Scheme 3) could be easily prepared from syn aldols generated from ketones **1**.[14] The preparation of chiral synthons of the d^3 class involve oxidative cleavage of one C−C bond of the initial erythrulose moiety. They thus preserve three of the four carbons of the sugar as well as the two newly generated stereogenic carbon atoms. Chiral synthons of the d^4 class, generated from aldols without C−C oxidative cleavage, are still more interesting from the point of view of atom economy[15] as they preserve all four erythrulose carbons together with the initially resident chirality. As shown in Scheme 3, *syn*,*syn*-stereotriads and *syn*,*syn*,*syn*-stereotetrads can be created in this way.

We thus wanted to expand this methodology to the anti aldols described here. With this purpose in mind, the previously used aldolization/in situ reduction sequence[14] was applied again. Thus, the *E* boron enolate generated from **5a** was added to isobutyraldehyde and benzaldehyde. Prior to the standard workup, $LiBH_4$ was added to the reactions mixture with the aim of performing an in situ stereoselective reduction to the corresponding syn 1,3-diol.[16] However, the anti 1,3-diols **8a**/**8b** were the sole compounds obtained (Scheme 4).[13,17] The two free hydroxyl groups in compounds **8a**/**8b** were then protected as the corresponding acetonides **9a**/**9b**. Selective cleavage of the primary silyl group to yield alcohols **10a**/**10b** took place under mild conditions using the hydrogen fluoride-pyridine complex. After mesylation of the alcohol function, the benzoate group was hydrolyzed by alkaline treatment. The intermediate hydroxy mesylates cyclized spontaneously to yield epoxides **11a**/**11b**. These are functionalized d^4 synthons with a syn/syn/anti relative arrangement of the oxygen atoms, thus diastereomeric to those depicted in Scheme 3.[14]

SCHEME 4. Synthesis of Functionalized d^3 and d^4 Chiral Synthons from Anti Aldols of Erythrulose Derivatives[a]



[a] Reagents and conditions: (a) Chx_2BCl, Et_3N, 0 °C, 1 h, then RCHO, −78 °C, 5 h, then $LiBH_4$, −78 °C, 2 h, then diastereomer separation (**8a**, 76%; **8b**, 74%); (b) acetone, 2,2-dimethoxypropane, CSA, 3 Å MS, rt, 12 h (**9a**, 87%; **9b**, 80%); (c) HF−pyridine, THF, rt, 6−12 h (**10a**, 79%; **10b**, 72%); (d) (1) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, (2) KOH/MeOH, rt, 1 h (**11a**, 72%; **11b**, 69%, overall yields for the two steps); (e) K_2CO_3, MeOH, rt, 1 h (**12a**, 83%; **12b**, 82%); (f) (1) PivCl, CH_2Cl_2-py, 0 °C, 30 min, (2) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, (3) KOH/MeOH, rt, 24 h (**13a**, 52%; **13b**, 48%, overall yields for the three steps); (g) $NaIO_4$, aq THF, rt, 1 h (**14a**, 93%; **14b**, 95%). Abbreviations: TBS, *tert*-butyldimethylsilyl; Chx, cyclohexyl; CSA, camphor-10-sulfonic acid; MsCl, methanesulfonyl chloride; Piv, pivaloyl.

Functionalized d^4 synthons **13a**/**13b** displaying the anti/syn/anti stereotetrad were obtained with the same methodology used in our previous paper.[14] Thus, after alkaline cleavage of the benzoate function in **10a**/**10b** to yield diols **12a**/**12b**, the primary hydroxyl group was

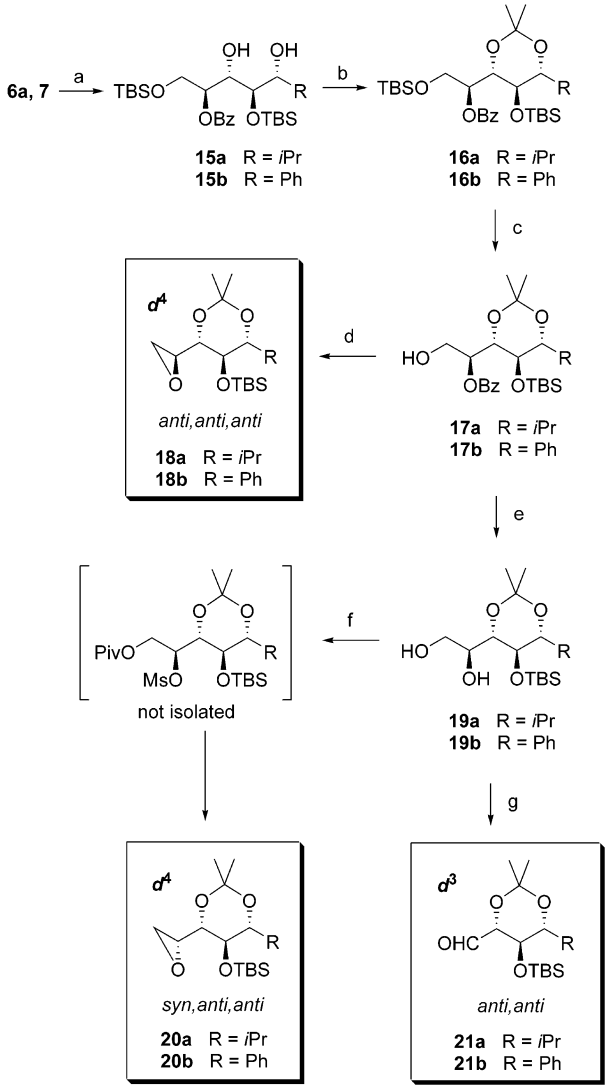
(14) Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 2317−2327.
(15) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705.
(16) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797−800.

selectively acylated as its pivalate ester. Mesylation of the secondary alcohol furnished the intermediate pivalate−mesylate (depicted in Scheme 4) which, without purification, was subjected to alkaline treatment. This caused hydrolysis of the pivaloyl moiety, followed by rapid closure to epoxides **13a**/**13b** via intramolecular displacement of the mesylate group with configurational inversion. Diols **12a**/**12b** served also as precursors of the functionalized d^3 synthons **14a**/**14b** (syn/anti stereotriad) via oxidative diol cleavage with sodium metaperiodate.

Further functionalized d^4 synthons with alternative stereochemical arrangements were obtained through a modification of the aldol reduction. This was not performed, however, in the expected manner. During our initial attempts to reduce the aldol in the anti mode, we subjected the isolated aldols to reduction with tetramethylammonium triacetoxyborohydride (TABH). This reaction, however, did not take the expected stereochemical course. Instead of the anticipated anti 1,3-diol,[18] treatment of aldols **6a** and **7** with TABH under the prescribed conditions gave rise to syn 1,3-diols **15a**/**15b** as the main compounds (dr ∼ 9:1) (Scheme 5).[13,19] Hereafter, we proceeded in the same manner described in Scheme 4. In this way, the functionalized d^4 synthons **18a**/**18b** and **20a**/**20b** displaying, respectively, the anti/anti/anti and the syn/anti/anti stereotetrads were obtained. Similarly, oxidative cleavage of diols **19a**/**19b** gave the functionalized d^3 synthons **21a**/**21b** with an anti/anti stereotriad.

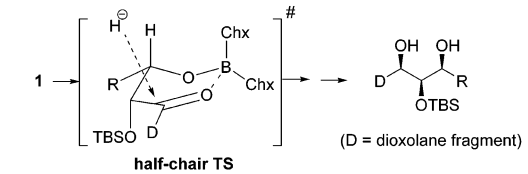
We now wish to illustrate the synthetic usefulness of the aforementioned methodology in the case of a chiral natural product. (+)-Goniothalesdiol **22** is a 2,3,4,5-tetrasubstituted tetrahydrofuran derivative isolated in 1998 from the bark of the Malaysian tree *Goniothalamus*

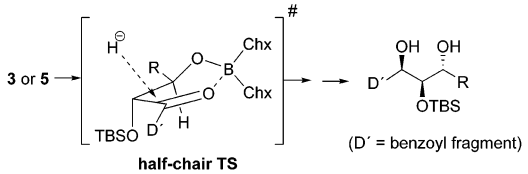
SCHEME 5. Synthesis of Further Functionalized d^3 and d^4 Chiral Synthons with Alternative Stereochemical Arrangements[a]



[a] Reagents and conditions: (a) TABH, AcOH/MeCN, −30 °C, 12 h (**15a**, 94%; **15b**, 84%, yields of the diastereomeric mixture); (b) acetone, 2,2-dimethoxypropane, CSA, 3 Å MS, rt, 12 h, then diastereomer separation (**16a**, 84%; **16b**, 83%); (c) HF−pyridine, THF, rt, 6−12 h (**17a**, 79%; **17b**, 73%); (d) (1) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, (2) KOH/MeOH, rt, 1 h (**18a**, 71%; **18b**, 69%, overall yields for the two steps); (e) K_2CO_3, MeOH, rt, 1 h (**19a**, 84%; **19b**, 84%); (f) (1) PivCl, CH_2Cl_2-py, 0 °C, 30 min, (2) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, (3) KOH/MeOH, rt, 24 h (**20a**, 48%; **20b**, 48%, overall yields for the three steps); (g) $NaIO_4$, aq THF, rt, 1 h (**21a**, 93%; **21b**, 94%). Abbreviations: TABH, tetramethylammonium triacetoxyborohydride (see also Scheme 4).

(17) This unexpected stereochemical outcome was previously observed in the in situ $LiBH_4$ reduction of aldol mixtures generated from ketone **3**: Carda, M.; Falomir, E.; Murga, J.; Castillo, E.; González, F.; Marco, J. A. *Tetrahedron Lett.* **1999**, *40*, 6845−6848. A plausible explanation of this unexpected stereochemical course is shown in the following transition states (TS). The syn boron aldolates formed from ketone **1** adopt a half-chair conformation where the bulky R group tends to be situated in an equatorial-like orientation (D = dioxolane fragment), thus avoiding a steric repulsion with the voluminous boron ligands. Attack of the external hydride donor ($LiBH_4$) takes place at the carbonyl *Si* face along a sterically uncrowded, and stereoelectronically favored, Felkin-Anh approach (anti to the OTBS group), with formation of the observed all-syn stereoisomer (*syn*-1,3-diol moiety). By the same line of reasoning, *anti*-aldolates formed from **3** or **5** also adopt a half-chair conformation with an equatorial-like R group (D′ = benzoyl-containing fragment). Once again, hydride attack at the carbonyl *Si* face becomes favored from both steric and stereoelectronic factors. However, this yields here an *anti*-1,3-diol moiety.





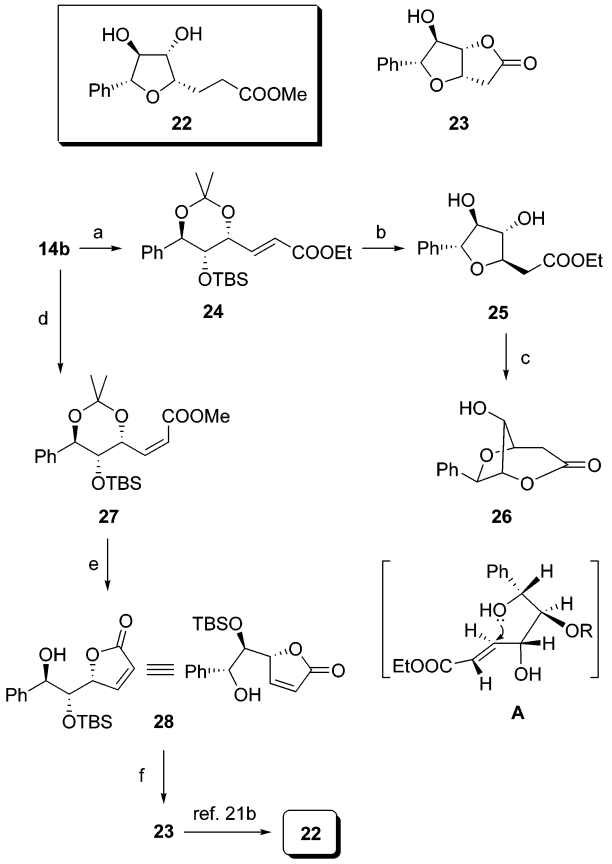
(18) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

borneensis (Annonaceae)[20] and found to exhibit a measurable cytotoxic activity against P388 mouse leukemia cells. Two syntheses of this bioactive metabolite have been published so far.[21] One of them used D-glucuronolactone as the starting material and finally provided (−)-goniothalesdiol, the enantiomer of the natural compound, through a lengthy 16-step reaction sequence.[21a] The other synthesis started from D-mannitol and required nine steps, one of them nonstereoselective (∼1:1 mixture of stereoisomers), to yield lactone **23**, subsequently converted into **22** by means of a few additional transforma-

tions.[21b] Compound **23** became here our synthetic target. The starting material was aldehyde **14b**, one of the d^3 syntons depicted in Scheme 4. Wittig-Horner-Emmons olefination of **14b** under mild conditions[22] furnished trans ester **24**. Hydrolytic treatment of the latter not only caused cleavage of the acetonide moiety and the TBS group but also in situ intramolecular Michael addition to yield tetrahydrofurane ester **25**. Acid treatment of the latter provided a lactone **26** which was different in its spectral properties from **23**. We concluded therefore that the intramolecular Michael addition took place with the undesired stereochemical course (Scheme 6).[23] Most likely, the molecule of the precursor adopts conformation **A** (R = H or TBS) for the Michael addition, where both torsional interactions between the chain substituents and allylic 1,3-strain are minimized.

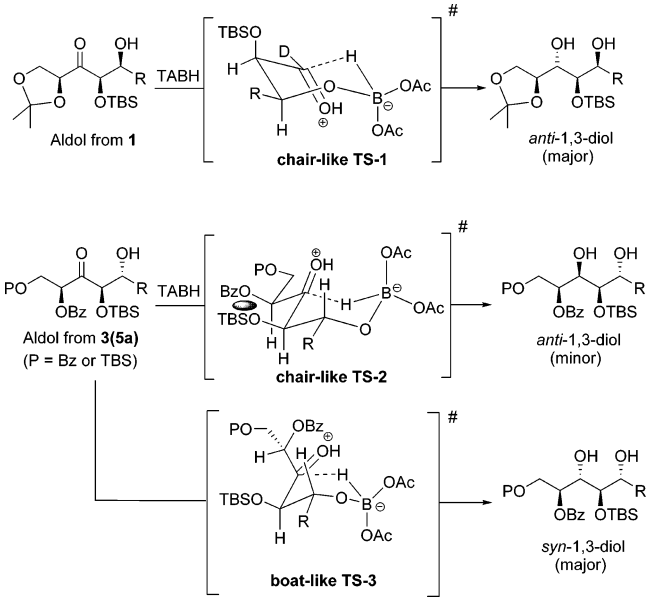
We then reasoned that the intramolecular Michael addition would be compelled to take the required stereochemical pathway provided that the process occurred in a precursor having already the lactone ring in place. Thus, *Z*-selective Still−Gennari olefination[24] of aldehyde **14b** furnished uneventfully ester **27**. Acid-catalyzed methanolysis of the acetonide ring was accompanied by spontaneous lactonization to **28**. Due to the steric constraints imposed by the lactone ring, the intramolecular Michael addition of the free hydroxyl to the conjugated

SCHEME 6. Formal Synthesis of (+)-Goniothalesdiol 22[a]



[a] Reagents and conditions: (a) $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, rt, 18 h (85%); (b) PPTS, MeOH, 50 °C, 18 h (62%); (c) CSA, tol, 80 °C, 12 h (70%); (d) $(CF_3CH_2O)POCH_2COOMe$, KHMDS, 18-crown-6, −78 °C, 30 min (86%); (e) PPTS, MeOH, 50 °C, 12 h (68%); (f) TBAF, THF, rt, 1 h (78%). Abbreviations: DIPEA, ethyl *N*,*N*-diisopropylamine; PPTS, pyridinium *p*-toluenesulfonate; tol, toluene; KHDMS, potassium hexamethyldisilylamide; TBAF, tetra-*n*-butylammonium fluoride hydrate (see also Schemes 4 and 5).

(19) As we reported in ref 14, TABH reduction of the syn aldols generated from ketone **1** takes place mainly in the expected anti manner, even though with a moderate stereoselectivity (~7:3). A possible explanation of the diverging stereochemical outcome with aldols from ketones **3** or **5a** is proposed below. The internal hydride transfer through a six-membered chairlike TS with the R group in equatorial orientation (depicted below as **TS-1** for aldols from **1**, D = dioxolane moiety), as proposed by Evans and co-workers (ref 18), faces important pentane gauche repulsive interactions in the case of aldols from **3** or **5a** (see the chairlike **TS-2**, which leads to the minor *anti*-1,3-diol). Note that a C−C bond rotation in **TS-2** may eliminate this gauche interaction but with simultaneous increase of the dipolar repulsion between the C=O and C−OBz bonds. As an alternative explanation, we propose the boatlike **TS-3**, where these unfavorable interactions are relieved in part, and which predicts the formation of the *syn*-1,3-diol. In any case, it is worth remembering here that TABH reductions of densely oxygenated α,α',*β*-chiral *β*-hydroxy ketones, such as those discussed here, are not extensively documented. In fact, cases of low diastereoselectivity in TABH reductions of α-alkyl-*β*-hydroxyketones are not unprecedented: Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655−14662.



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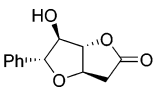
(23) Had the Michael addition taken the desired course, the resulting tetrahydrofurane ester would necessarily have cyclized to lactone **23**, as no other alternative is available. Since lactone **26** was synthetically useless, no efforts were invested in the unambiguous establishment of its structure via exhaustive NMR measurements. Theoretically, ester **25** might also have cyclized to bicyclic lactone **i**. However, the strained *trans*-fused dioxabicyclo[3.3.0]octane system of the latter makes this a less likely alternative. In fact, the predicted values for the ^{1}H NMR vicinal coupling constants in **26** (^3J = 0−3 Hz, according to modelization with PCMODEL) were very similar to the experimental values (<2 Hz), in contrast with lactone **i**, where calculated values for ^3J were always >7 Hz.



i

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C═C bond was anticipated to take necessarily the desired stereochemical course and yield an unstrained *cis*-fused dioxabicyclo[3.3.0]octane system. Indeed, treatment of **28** with tetra-*n*-butylammonium fluoride not only caused the expected desilylation but also induced an in situ cyclization to yield lactone **23**, identical in its spectral properties with the described compound.[21b] Since **23** has already been converted into (+)-goniothalesdiol **22**, this constitutes a formal synthesis of this natural compound (Scheme 6). The synthesis is not only comparatively short but also highly stereoselective in each of its steps.

Conclusions

We have shown that anti aldols can be efficiently obtained from a protected erythrulose derivative, in turn readily available from L-erythrulose in only two steps. Furthermore, various chiral, polyoxygenated d^3 and d^4 synthons can be easily prepared in few steps from the aforementioned anti aldols. These synthons display the same functional arrays as those prepared from the previously reported syn aldols[14] but show different stereochemical features. We have also shown that such synthons are very useful in the synthesis of polyoxygenated molecules and have demonstrated it with the example of the bioactive metabolite (+)-goniothalesdiol. Further investigations related to synthetic uses of the aforementioned chiral synthons are underway and will be reported in due course.

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Supporting Information Available: Detailed experimental procedures; complete analytical and spectral data of ketones **5a**−**c** and aldols **6a**−**c** and **7**; description of correlation procedures and spectral data of compounds **8**−**21** and **23**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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