Asymmetric Synthesis

DOI: 10.1002/anie.200900609

Stereocontrolled Synthesis of Highly Functionalized Quaternary Carbon Centers: A Route to α-Substituted Serines**

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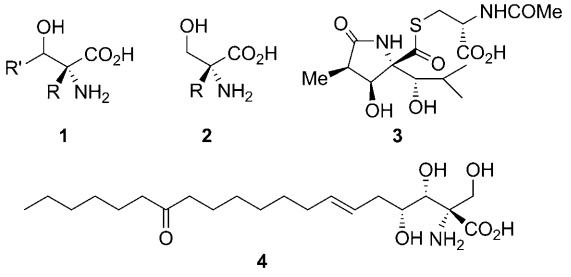
In memory of Xavier Solans

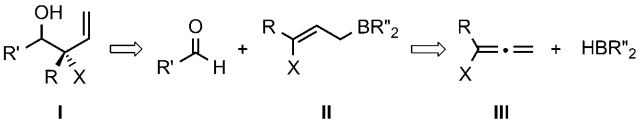
The development of efficient stereoselective methods for the formation of C–C bonds involving the construction of a quaternary carbon centre has attracted much attention.[1] These processes become more useful and challenging if additional neighboring stereogenic centers and polar functionalities are also formed stereoselectively. In this context, our research group is interested in developing methodologies for the construction of substructures bearing a densely functionalized quaternary center; like those found in α-substituted threonines **1** or serines **2**,[2] as well as in more complex natural products of biological relevance such as the proteasome inhibitor lactacystin (**3**)[3] or the immunosuppressant myriocin (**4**).[4]



1 **2** **3**

4

We envisaged that quaternary amino acids such as **1** or **4** could arise from a homoallylic alcohol **I** which, in turn, could be obtained by the stereoselective addition of a substituted allylic organoborane **II** to an aldehyde (Scheme 1). Despite the extensive use of various terpene- and tartrate-based chiral



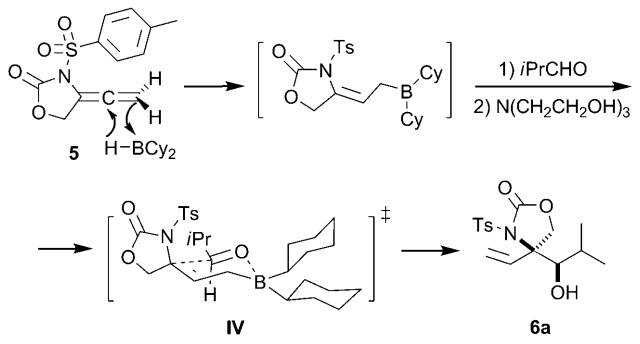
I **II** **III**

(X=protected N or heteroatom)

Scheme 1. Retrosynthetic analysis of **I**.

allylborane as well as crotylborane reagents,[5] the required stereoselective addition of γ,γ-disubstituted allylboranes to aldehydes has been much less explored.[6] Examples of the stereoselective creation of quaternary carbon centers by addition of γ-heteroatom allylboranes such as **II** are still scarce.[7] The limited use of such γ,γ-disubstituted allylboranes in organic synthesis is probably due to the difficulty involved in their stereoselective preparation. To overcome this drawback, we anticipated that **II** could be prepared in a straightforward manner by hydroboration of allene **III**.

Our initial proposal for **III** was allene **5**, since it can be easily obtained in two steps from but-2-yn-1,4-diol (Scheme 2).[8] We reasoned that its hydroboration at the less hindered face of the terminal double bond would generate an unsymmetrical *Z* allylborane, which could be stereoselectively added to an aldehyde to generate the amino diols **6** that are protected at the quaternary center. To our delight, we found that the treatment of **5** with dicyclohexylborane in



5 **IV** **6a**

Scheme 2. Synthesis of **6a** by addition of **5** to isobutyraldehyde. Cy = cyclohexyl, Ts = 4-toluenesulfonyl.

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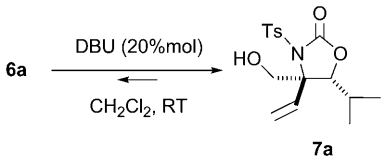
[**] This work has been supported by the Ministerio de Educación y Ciencia (BQU2003-01269 and CTQ2006-13249). We thank the Generalitat de Catalunya for a doctorate studentship to C.S. and J.O.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900609.

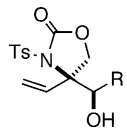
CH_2Cl_2 at room temperature, and subsequent addition of a slight excess of isobutyraldehyde at −78 °C afforded **6a** as a single stereoisomer in 74% yield.[9,10]

Interestingly, in the presence of a catalytic amount of DBU in CH_2Cl_2 at room temperature, **6a** exhibited an equilibrium largely shifted towards its regioisomer **7a**, which was readily isolated in 85% yield after column chromatography.[11] One-dimensional nuclear Overhauser enhancement experiments on **7a** enabled us to determine its relative configuration, which is shown in Scheme 3.



Scheme 3. Isomerization of **6a** to **7a**. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

These remarkable results prompted us to extend this reaction to a series of representative aldehydes. As shown in Figure 1, good to excellent yields of **6b–h** were obtained with



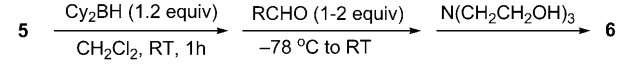
6a R = *i*Pr	74%	**6e** R = CH=CH$_2$	80%
6b R = Et	81%	**6f** R = C≡C−C$_5$H$_{11}$	81%
6c R = Ph	70%	**6g** R = CH$_2$OBn	78%
6d R = 2-Furyl	66%	**6h** R = H	60%

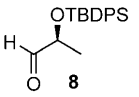
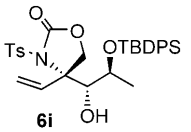
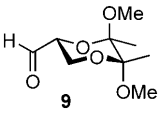
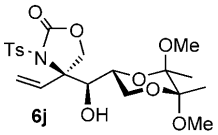
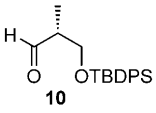
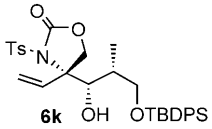
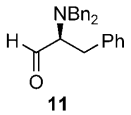
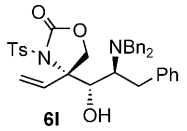
Figure 1. Compounds **6** prepared from achiral aldehydes and allene **5**. Bn = benzyl.

greater than 95% diastereomeric purity.[12] Only small amounts of compounds **7** (arising from **6** by migration of the carbamate group in the work-up and/or chromatographic purification) were observed. NOESY experiments on samples of **7b–g** confirmed the relative configuration assigned to **6a**, which can be rationalized though a transition state similar to **IV** in the addition step (see Scheme 2).

Seeking to obtain enantioenriched compounds by this process, we reasoned that obvious methods to use would be either a chiral dialkylborane in the hydroboration step or to use an enantiopure aldehyde. As a series of experiments using $(Ipc)_2BH$ (Ipc = isopinocampheyl) or dilongifolylborane led to moderate yields and low stereoselectivities we therefore turned our attention to using chiral aldehydes. Once more, excellent yields were obtained with representatives chiral aldehydes derived from (*S*)-lactaldehyde (**8**; Table 1, entry 1), (*R*)-glyceraldehyde (**9**; entry 2),[13a–c] (*R*)-3-hydroxy-2-methylpropanal (**10**; entry 3), and (*S*)-phenylalaninal (**11**; entry 4),[13d,e] even when a 1:1 ratio of allene to aldehyde was used (entry 1). Notably, the stereofacial selectivity for aldehydes **8** and **9** was very high as only one stereoisomer was detected by ^{1}H NMR spectroscopy. The stereoselectivity observed for aldehydes **10** and **11** was also high (10:1 and 8:1, respectively).

Table 1: Tandem hydroboration of **5** and addition of chiral aldehyde to give the enantioenriched, protected amino diols **6i–l**.

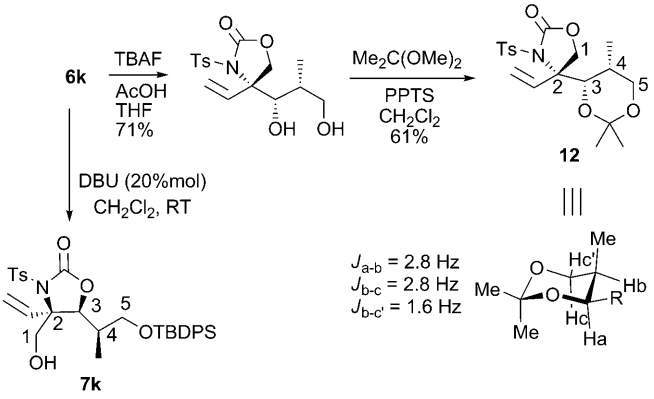


Entry	Aldehyde	Adduct	Yield [%][d]
1[a]	 **8**	 **6i**	95
2[b]	 **9**	 **6j**	90
3[b]	 **10**	 **6k**	80
4[c]	 **11**	 **6l**	74

[a] 1 equivalent of aldehyde was used. [b] 2 equivalents of aldehyde were used. [c] 1.4 equivalents of aldehyde were used. [d] Yield of isolated product. TBDPS = *tert*-butyldiphenylsilyl.

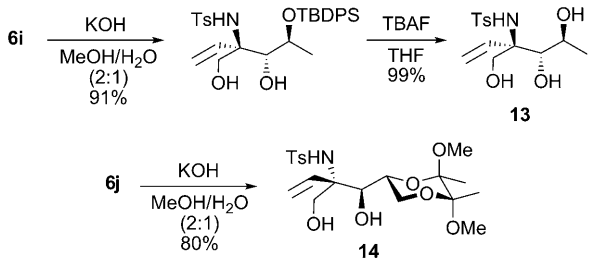
The relative configuration of **6k** was determined by ^{1}H NMR experiments of derivatives **7k** and **12** (Scheme 4). Thus, **6k** was easily transformed into the 1,3-diol acetonide **12**. The *syn* relationship of the new stereocenter at C3, relative to the *R* configuration of C4 in the starting aldehyde, was ascertained by analyzing the vicinal proton coupling constants of the dioxolane ring.[14] Meanwhile, NOESY experiments on compound **7k**, which was readily obtained by isomerization of **6k** in basic media, allowed us to establish the configuration shown in Scheme 4.

To determine the absolute configuration of adducts **6i** and **6j** we sought to transform them into crystalline derivatives. Thus, the silicon protecting group was selectively removed



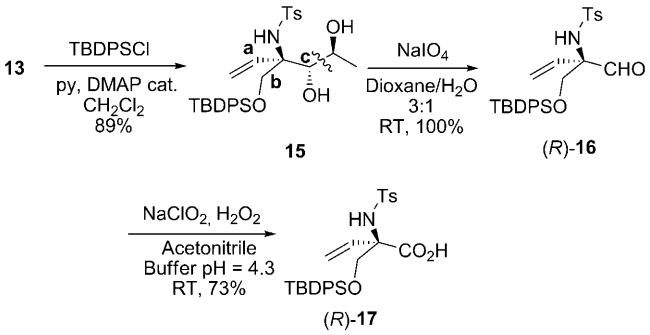
Scheme 4. Preparation of derivatives **7k** and **12** from **6k**. PPTS = pyridinium 4-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

using HF or TBAF and the carbamate rings were hydrolyzed in basic media. The resulting polyols **13** and **14** were easily crystallized and their corresponding single-crystal X-ray analysis agreed with the configurations shown in Scheme 5.[15,16]



Scheme 5. Preparation of derivatives **13** and **14** from **6i** and **6j**.

Indeed, we envisaged that enantiopure **13** (or its enantiomer arising from (*R*)-lactaldehyde) could be a versatile starting material for the synthesis of quaternary α-amino-β-hydroxyacids. Remarkably, the three carbon substituents (**a**–**c**) in **15** that are attached to the quaternary centre are amenable to transformation into either a carboxylic acid or a hydroxymethyl group (Scheme 6). In particular, selective protection of the primary alcohol with a *tert*-butyldiphenylsilyl group, and subsequent oxidative cleavage of the 1,2-diol moiety afforded aldehyde (*R*)-**16**, which was easily trans-



Scheme 6. Stereoselective synthesis of protected α-vinylserine. DMAP = 4-dimethylaminopyridine, py = pyridine.

formed to the corresponding protected α-vinylserine (*R*)-**17**. It is worth noting that α-vinylserines are competitive inhibitors of serine hydroxymethyl transferase.[17,18]

In conclusion, we have established a new approach to afford highly functionalized quaternary aminopolyols in which two adjacent stereocenters are formed with high stereoselective control. The use of chiral α-substituted aldehydes provided the highly functionalized enantiopure building blocks **16** and **17** in excellent yields. These adducts are expected to have important applications in the synthesis of quaternary α-amino-β-hydroxyacids.

Received: February 2, 2009
Revised: March 26, 2009
Published online: May 4, 2009

Keywords: allenes · amino alcohols · asymmetric synthesis · boranes · substituted serines

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[10] As expected, *Z* allyldicyclohexylborane does not seem to undergo isomerization to its *E* isomer at room temperature. In this case, the known boratropic allylic rearrangement that causes *Z*/*E* isomerisation in crotyldialkylboranes seems to be inhibited by steric hindrance. In fact, when the hydroboration step was performed in CH_2Cl_2 at reflux, the same single stereoisomer was obtained, albeit in lower yield.

[11] Isomerization of **6a** to **7a** was not surprising as related base-catalyzed processes that involve *N*-acyl or *N*-alkyl cyclic carbamates have been reported in the literature: a) W. R. Roush, M. A. Adam, *J. Org. Chem.* **1985**, *50*, 3752–3757; b) D. L. Boger, M. W. Ledeboer, M. Kume, *J. Am. Chem. Soc.* **1999**, *121*, 1098–1099; c) S. P. Bew, S. D. Bull, S. G. Davies, E. D. Savory, D. J. Watkin, *Tetrahedron* **2002**, *58*, 9387–9401.

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[15] The observed configuration agrees with that expected from the transition state **IV** shown in Figure 1, in which the chiral aldehyde is arranged according to the Felkin–Anh model. For a review on the addition of achiral allylboron reagents to chiral aldehydes, see: W. R. Roush in *Methods of Organic Chemistry (Houben-Weyl)*, *Vol. E21* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp. 1430 – 1439; for a review on Cram's and Felkin–Anh models, see: A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191 – 1223.

[16] X-ray quality crystals of **13** and **14** were grown by slow evaporation of a dichloromethane solution. Compound **13**: ($C_{14}H_{21}NO_5S$): $0.2\times0.1\times0.1$ mm; orthorhombic $P2_12_12_1$; $a=6.118(3)$, $b=13.304(4)$, $c=18.982(6)$ Å; $V=1545.0(10)$ Å^3 ($Z=4$); $\rho_{calcd}=1.356$ Mg m^{-3}; $2\theta_{max}=28.37°$; $-7<h<8$, $-16<k<16$, $-24<l<25$; $\lambda=0.71073$ Å; $T=293$ K; no. reflections = 10353; no. independent reflections = 3261 (R(int) = 0.0574); restraints/parameters = 11/207; full-matrix least-squares refinement on F^2; no. absorption correction; $\mu=0.230$ mm^{-1}: final R indices ($I>2\sigma(I)$) are $R_1=0.0375$ and $wR_2=0.0988$: largest diff. Peak and hole = 0.291 and -0.328 e Å^{-3}. Compound **14**: ($C_{20}H_{31}NO_8S$): $0.19\times0.18\times0.16$ mm: monoclinic $P2_1$; $a=11.879(7)$, $b=7.824(4)$, $c=12.470(4)$, $\beta=109.55(2)°$; $V=1092.2(9)$ Å^3 ($Z=2$); $\rho_{calcd}=1.355$ Mg m^{-3}; $2\theta_{max}=30.00°$; $17<h<17$, $-9<k<10$, $-17<l<18$; $\lambda=0.71073$ Å; $T=293$ K; no. reflections = 12395; no. independent reflections = 5757 (R(int) = 0.0526); restraints/parameters = 7/277; full-matrix least-squares refinement on F^2; no. absorption correction; $\mu=0.194$ mm^{-1}; final R indices ($I>2\sigma(I)$) are $R_1=0.0558$ and $wR_2=0.1393$: largest diff. Peak and hole = 0.370 and -0.314 e Å^{-3}. CCDC 707178 (**13**) and 707179 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] A sample of (*R*)-**17** was converted into (*R*)-α-vinylserine by sequential removal of the TBDPS (TBAF·3 H$_2$O, THF) and tosyl (naphthalene, Na, DME(1,2-dimethoxyethane)/THF 1:1) protecting groups. The spectroscopic data of the amino acid obtained were identical to those reported in Ref. [17b].

