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One-pot synthesis of (3*R*)-hydroxy-β-lactams via enolates of 2-*tert*-butyl-1,3-dioxolan-4-ones. Part 1 †

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Abstract: Seebach's synthetic method of self-regeneration of stereocenters "SRS" has been applied to the addition reaction of diphenylimine **1** to the lithium enolates of (*2S,5S*)-2-(*tert*-butyl)-5-methyl-1,3-dioxolan-4-one **2a** and of (*2S,5S*)-2-(*tert*-butyl)-5-phenyl-1,3-dioxolan-4-one **2b**. Variable *4S/4R* mixtures of (*3R*)-3-hydroxy-β-lactams **4a,b** are obtained, depending on the reaction conditions. The induced enantioselectivity (*ee*) is very high, and the simple selectivity (exo–endo) is low. Overall, this appears a rather direct approach to chiral β-lactams with full control of stereochemistry at C3. The stereoselective radical reduction of the stereoisomer (*3R,4R*)-*E*-**4a** afforded the homochiral C3,C4-monosubstituted β-lactam (*3S,4S*)-*Z*-**10**. © 1997 Elsevier Science Ltd

The synthesis of β-lactams with control of absolute stereochemistry has long been attracting the interest of organic chemists not only due to the biological activity of these synthetic targets, but also to their use as intermediates for synthesis of natural and unnatural products. Natural, or readily available "chiral pool" compounds for synthesis of β-lactams are, for example, β-hydroxyamides and β-aminoacids. We believe that also α-hetero-substituted carboxylic acids, such as α-hydroxy-, α-mercapto-, and α-aminoacids, are inexpensive natural chiral pool material which could be used even for industrial-scale applications for the synthesis of β-lactams with absolute stereocontrol at the C3 quaternary center bearing interesting functional groups, such as OR, SR, NHR. This is very important since the substituents affect the biological activity of these heterocycles. As an example, the presence of a 3-methoxy substituent as part of a quaternary stereogenic center at the C3 carbon atom of the 3-methoxy-3-amino-monobactamic acid increases the β-lactamase stability with respect to the C3-mono-substituted 3-amino-monobactamic acid.[1] On the other hand, studies of the structure–activity relationship on β-lactams with a defined stereochemistry in a quaternary center at C3 are lacking due to the inherent difficulties in their synthesis. To achieve the target of full control of stereochemistry in a quaternary stereogenic center of 3-hydroxy-β-lactams we have devised a strategy which employs imines as the electrophilic partners of enolates of acetal-type derivatives of chiral α-hydroxy-substituted carboxylic acids. This strategy follows the synthetic principle called "Self-regeneration of Stereocenters" (SRS), developed by Seebach,[2] which has been used for EPC[3] alkylations and aldol condensations of these enolates. To our knowledge, the imines have not yet been employed as the electrophilic partners in "SRS" type reactions. Here we report a detailed investigation of the addition reaction of diphenylimine **1** to the thermally unstable lithium enolate of the (*2S,5S*)-2-(*tert*-butyl)-5-methyl-1,3-dioxolan-4-one **2a** and to the more stable enolate of the (*2S,5S*)-2-(*tert*-butyl)-5-phenyl-1,3-dioxolan-4-one **2b**. In this initial model study, a diastereomeric (*2S,5S*)-*cis*/(*2R,5S*)-*trans*=97:3 mixture of **2a**[4b] was converted into the corresponding enolates (*2S*)-**3a** and (*2R*)-**3a** by reaction with lithium diisopropyl-amide (LDA) in THF at −78°C (method A). The condensation with the imine **1**,

† Dedicated to Professor Dr. Dieter Seebach, ETH Zürich, on the occasion of his 60th birthday.

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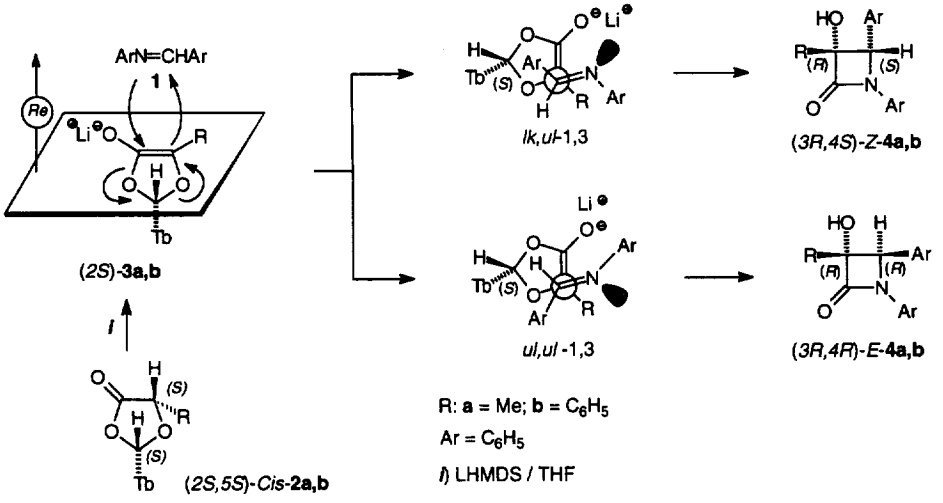
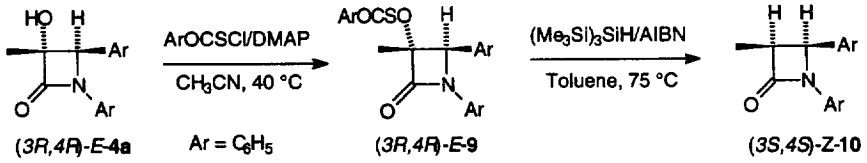
the cyclization, and the elimination of the auxiliary center occurred in a one step sequence providing directly a *Z*/*E*=64:36 mixture of β-lactams **4a** in 34% overall yield (Scheme 1).[5] Chiral HPLC analysis[6] showed that both diasteroisomers were obtained as enantiomer couples in 97:3 ratio, 94% *ee*. This result indicated that the cycloaddition occurred under total facial-diastereocontrol since the obtained 94 *ee* corresponds to the expected one. We assigned a (*3R,4S*)-*Z* and a (*3R,4R*)-*E* stereoconfiguration to the two major isomers which were derived from enolate (*2S*)-**3a** (97%) and (*3S,4R*)-*Z* and a (*3S,4S*)-*E* to the corresponding enantiomers derived from (*2R*)-**3a** (3%).



Scheme 1. Formation of β-lactams (*3R,4S*)-*Z*-**4a,b** and (*3R,4R*)-*E*-**4a,b** from the reaction of dioxolanone (*2S,5S*)-*cis*-**2a,b** and imine **1**.

The assignment of *R* configuration to the C3 stereogenic center of (*3R,4S*)-*Z*-**4a** and of (*3R,4R*)-*E*-**4a** is made on the assumption that the attack of the imine occurs from the face opposite to the *tert*-butyl substituent. Since the *cis*-configuration was assigned to the major dioxolanone **2a**, the two β-lactams are related to the *cis*-**2a** reagent through a retention mode at C3. In particular, compound (*3R,4S*)-*Z*-**4a** is formed when the enolate (*2S*)-**3a** and **1** approach with a relative *lk,ul*-1,3 topicity, while (*3R,4R*)-*E*-**4a** is derived from a relative *ul,ul*-1,3 topicity. After separation of the two diasteroisomers the relative *Z* and *E* configuration of the C3-Me and the C4-H substituents of (*3R,4R*)-*E*-**4a** and (*3R,4S*)-*Z*-**4a** was assigned by qualitative homonuclear NOE difference spectra. In particular, the irradiation of the C4-H signal centered at 5.0 ppm of (*3R,4S*)-*Z*-**4a** showed a large enhancement (9%) of the neighboring methyl protons (C3-Me) centered at 1.7 ppm. The absolute configuration of (*3R,4R*)-*E*-**4a** was confirmed by chemical correlation with the β-lactam 1,4-diphenyl-3-methylazetidinone (*3S,4S*)-*Z*-**10** (Scheme 2).



Scheme 2.

Treatment of (*3R,4R*)-*E*-**4a** with phenyl chlorotionocarbonate in acetonitrile with 4-dimethylaminopyridine (DMAP) catalyst[7] afforded (*3R,4R*)-*E*-**9** in 30% yield together with unreacted (*3R,4R*)-*E*-**4a** and other side-products. After purification by flash chromatography (SiO_2/toluene), the radical diastereoselective reduction of β-lactam (*3R,4R*)-*E*-**9** with $(Me_3Si)_3SiH$ (TTMSS) under

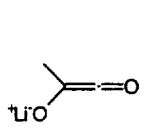
Table 1. Formation of β-lactams **4a,b**

Entry	**3** (*S/R*)	Procedure[a] (Base)	T°C (hrs)	Product	*3R,4S/3R,4R* (Yield %, *ee* %)	Byproducts (%)
1	**a** (97:3)	A[b] (LDA)	-78 /-50 (2)	**4a**	64 : 36 (34, 94[d])	**6** (12), **7**, (18), **8** (36)
2	**a** (97:3)	B[c] (LDA)	-90/-80 (7)	**4a**	20 : 80 (50, 94[d])	**8** (50) (**4** /**8** = 1:1)
3	**a** (97:3)	B[c] (LHMDS)	-90/-80 (8)	**4a**	18 : 82 (69, 94[d])	**8a** (24) (**4/8** = 3:1)
4	**b** (*S*)	A[b] (LDA)	+5 (10)	**4b**	*3R,4S* (65, 51[e])	
5	**b** (*S*)	B[c] (LHMDS)	-50 (3)	**4b**	23:77 (82, 99[e])	

(a) Order of addition of the reagents. Procedure A: *i)* **2**, *ii)* **Base**, *iii)* **1**; Procedure B: *i)* **Base**, *ii)* **1**, *iii)* **2**; (b) Solvent: THF; (c) Solvent: THF/HMPA= 85:15; (d) Expected *ee* = 94; (e) Expected *ee* = 100.

azo-bis(isobutyronitile) (AIBN) catalysis in toluene at 75°C gave the homochiral β-lactam (*3S,4S*)-*Z*-**10**, exclusively. The relative[8] and the absolute[9] configurations of (*3S,4S*)-*Z*-**10** were determined by comparison of the ^{1}H NMR spectral data and CD spectra, respectively, with the data reported in the literature.

A careful analysis of the reaction mixture revealed the presence of unexpected products **6**, **7**, and **8** in a ratio *Z*-**4a**:*E*-**4a**:**6**:**7**:**8**=22:12:12:18:36 (entry 1, Table 1 and Scheme 3). The amide **6** is derived from a competitive thermal decompostion of the enolate during the reaction to give pivalaldehyde and ketene **5**. The ketene was trapped by diisopropylamine (or LDA) to afford **6**.[10] Compound **7** is derived from a self-addition of the dioxolanone **2a** to the enolate **3a**.[4a] Finally, the lactone alcohol **8** is formed from the addition reaction of enolate **3a** with pivalaldehyde.[4a] Formation of **6** and **7** was avoided by adding the lactone **2a** to a mixture of LDA and imine **1** (procedure B) and by conducting the reaction at −95°C in a mixed solvent THF/HMPA=85:15 (entry 2) providing a 10:40:50 mixture of *Z*-**4a**:*E*-**4a**:**8**. Also this reaction occurred under total facial diastereocontrol since a 94% *ee* was measured for both β-lactams. The formation of equimolar amounts of β-lactams and lactone alcohol **8** indicates that the enolate is quantitatively trapped by the pivalaldehyde which is very rapidly formed after the initial attack of the imine **1** to the enolate. Nevertheless, overall yield in β-lactams was increased to 76% by performing the reaction of entry 2 using hexamethyldisilazide (LHMDS)[11] as the deprotonating agent instead of LDA (entry 3, *Z*-**4a**:*E*-**4a**:**8**=14:62:24). It is worth noting that when the reaction is performed in the mixed solvent, an inversion of diastereoselectivity is noticed and compound (*3R,4R*)-*E*-**4a** becomes the major isomer.[12] Control experiments demonstrated that no *Z/E* epimerization occurred under the basic reaction conditions and in the presence of the polar hexamethylphosporic triamide (HMPA).



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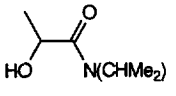

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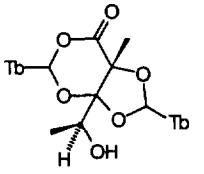

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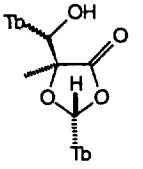

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Scheme 3. Byproducts of the reaction of dioxolanone (*2S,5S*)-*Z*-**2a** and imine **1**.

The reaction of **1** and homochiral enolate (*2S*)-**3b**, derived from dioxolanone[4a] (*2S,5S*)-*Z*-**2b**, at 5°C according to procedure A, gave the β-lactam (*3R,4S*)-*Z*-**4b** in 65% yield and 51% *ee*. The poor

enantioselectivity is probably due to the high reaction temperature which favored the collapse of the enolate to give hydroxyphenylketene and sequential formation of (*Rac*)-*Z*-**4b**. By contrast, an increase of enantioselectivity was observed when the reaction was performed at lower temperatures. In fact, the reaction of **1** and (*2S*)-**3b** at −50°C, according to procedure B, afforded a 23:77 *Z/E* mixture of β-lactams **4b** in 82% yield and 99% *ee* (100% expected). The relative configuration, *Z* and *E*, of the **4b** samples was assigned by comparison of their physical and spectral proprieties with those reported for the racemic forms.[13] Further, the absolute configuration *3R,4S* and *3R,4R* of the *Z*- and *E*-**4b** β-lactams was assigned on the basis of their CD spectra, as compared to those of (*3R,4S*)-*Z*-**4a** and (*3R,4R*)-*E*-**4a** compounds. This is also in agreement with the proposed mechanism for the attack of the imine to the enolates (*2S*)-**3a,b**.

Overall this methodology appears a rather direct approach to chiral β-lactams with a full control of stereochemistry at the C3 carbon atom.[14] This open a new strategy for the design and synthesis of new modified antibiotics which can improve biological activity and resistance toward enzymatic degradation.[15]

Acknowledgements

We thank the "Progetto Strategico Tecnologie Chimiche Innovative" of the CNR of Italy for financial support.

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2. For a leading reference dealing with the "SRS" principle see: Seebach, D.; Sting A. R.; Hoffmann. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708–2748. According to this principle a substituent at a stereogenic center of a chiral molecule is replaced without racemization and without the use of a chiral auxiliary. This has been accomplished in a four step sequence, i.e.: (a) a temporary stereogenic center is generated diastereoselectively, (b) the original stereogenic center is trigonalized by removal of a substituent, (c) a new ligand is introduced diastereoselectively, (d) the temporary center is finally removed.
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4. (a) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324. (b) Chapel, N.; Greiner, A.; Ortholand, J. Y. *Tetrahedron Lett.* **1991**, *40*, 1441–1442.
5. There is some confusion when the term *cis/trans* is used to define the relative configuration of 3-hydroxy-β-lactams which bear a quaternary stereogenic center at C3. For instance, according to Newcomb the β-lactams (*3R,4S*)-*Z*-**4a,b** are *cis*-isomers, instead, according to Palomo are *trans*-isomers. To avoid this confusion, we have used, according to the nomenclature used by Bose, the terms *Z/E* instead of *cis/trans*. See: (a) Gluchowski, C.; Cooper, L.; E. Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413–3416. (b) Palomo, C.; Cossio, F. P.; Odiozola, J. M.; Oiarbide, M.; Ontoria, J. M. *J. Org. Chem.* **1991**, *56*, 4418–4428. (c) Bose, A. K.; Lal, B.; Dayal, B.; Manhas, M. S. *Tertrahedron Lett.* **1974**, *30*, 2633–2636.
6. HPLC: Column Chiralpack AD (Daicel 250×4.0 mm). The mobile phase was *n*-hexane/2-propanol (90:10, 80:20, 50:50, v/v), 0.8 or 1.0 mL/min flow. The chromatographic retentions of the solutes were followed by a JASCO multi-340 multi channel detector. The eluates were also monitored by using a JASCO J 710 spectro-polarimeter (set at 250 nm) equipped with a micro HPLC cell. This detection system allows the absorption and the circular dichroism (CD) signals to be simultaneously detected. CD measurements were carried out by a J600 spectropolarimeter (c=0.4 mM, EtOH).
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9. As expected on the basis of the literature data, the circular dichroism spectrum of β-lactam (*3S,4S*)-*Z*-**10** was negative at 240 nm. See: Galle, D.; Tolksdorf, M.; Braun, M. *Tetrahedron Lett.* **1995**, *36*, 4217–4220. This result allowed the assignment of absolute configuration of (*3R,4R*)-*E*-**4a**.
10. Also the thermal decompostion of the lithium enolate of the (*2S,5S*)-2-(*tert*-butyl)-5-isopropyl-1,3-dioxolan-4-one afforded the corresponding 2-hydroxy-2,*N*,*N*-trimethylbutyramide. See: Ogawa, T.; Niwa, H.; Yamada, K. *Tetrahedron* **1993**, *49*, 1571–1578.
11. LHMDS is also recommended in the alkylation of a number of dioxolanones, to avoid the addition of pivalaldehyde to the corresponding enolates.
12. An identical result was obtained when 1,3-dimethyl-3,4,5,6-tetrahydro-2-(*1H*)-pyrimidone (DMPU), instead of HMPA, was used.
13. (a) Cossio, F. P.; Palomo, C. *Tertrahedron Lett.* **1985**, *35*, 4239–4242. (b) Bose, A. K.; Dayal, B.; Manhas, M. S; Kapur, J. C.; Lal, B. *Tertrahedron Lett.* **1974**, *36*, 3135–3138. (c) See Gluchowski *et al.*[5a]
14. It is worth noting that both enantiomers are available if either one of the enantiomeric starting α-hydroxyacids or if either one of the *cis*- or the *trans*-dioxolanones are available.
15. Analytical data of compounds **4**, **9** and **10** (only the relevant ^{13}C NMR resonances are given): **4a**: IR ($CDCl_3$): 1745 cm^{-1}; MS: *m/z* 253 (M^+), 181, 119. (*3R,4R*)-*E* (94% *ee*): $[\alpha]_D^{19}$ −134.0 (c=0.67, $CHCl_3$); mp 171–172°C; ^1H NMR ($CDCl_3$) δ 1.1 (s, 3), 4.0–4.3 (b, 1), 5.1 (s, 1), 6.9–7.4 (m, 10); ^{13}C NMR ($CDCl_3$) δ 18.4, 69.3, 85.8, 169.1. Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.73; H, 5.92; N, 5.57. (*3R,4S*)-*Z* (94% *ee*): $[\alpha]_D^{19}$ +125.8 (c=0.67, $CHCl_3$); mp 178–179°C; ^1H NMR ($CDCl_3$) δ 1.7 (s, 3), 2.5–2.7 (b, 1), 5.0 (s, 1), 7.0–7.4 (m, 10); ^{13}C NMR ($CDCl_3$) δ 21.7, 68.9, 83.5, 168.5. Anal. Found: C, 75.94; H, 6.03; N, 5.48. **4b**: IR ($CDCl_3$): 1750 cm^{-1}; MS: *m/z* 315 (M^+), 196, 181, 119. (*3R,4R*)-*E* (99% *ee*): $[\alpha]_D^{19}$ −1.1 (c=1.35, $CHCl_3$); mp 183–185°C; ^1H NMR ($CDCl_3$) δ 3.4–3.8 (b, 1), 5.35 (s, 1), 7.0–7.6 (m, 15); ^{13}C NMR ($CDCl_3$) δ 73.5, 85.2, 167.0. Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 80.12; H, 5.38; N, 4.47. (*3R,4S*)-*Z* (99% *ee*): $[\alpha]_D^{19}$ +52.6 (c=0.70, $CHCl_3$); mp 188–190°C; ^1H NMR ($CDCl_3$) δ 3.5–3.9 (b, 1), 5.27 (s, 1), 7.0–7.6 (m, 15); ^{13}C NMR ($CDCl_3$) δ=70.3, 86.8, 166.9. Anal. Found: C, 79.90; H, 5.40; N, 4.40. (*3R,4R*)-*E*-**9**: IR ($CDCl_3$): 1764, 1200 cm^{-1}; MS: *m/z* 329 (M^+−60), 181, 119. $[\alpha]_D^{19}$ −118.3 (c=0.48, $CHCl_3$); mp 186–187°C; ^1H NMR ($CDCl_3$) δ 1.56 (s, 3), 5.78 (s, 1), 7.0–7.6 (m, 15); ^{13}C NMR ($CDCl_3$) δ=73.5, 85.2, 167.0. Anal. Calcd. for $C_{23}H_{19}NO_3S$: C, 70.93; H, 4.92; N, 3.60. Found: C, 70.86; H, 4.98; N, 3.62. (*3S,4S*)-*Z*-**10**: IR ($CDCl_3$): 1760 cm^{-1}; MS: *m/z* 237 (M^+), 181, 119; $[\alpha]_D^{19}$ −221.0 (c=0.32, $CHCl_3$); mp 144–145°C; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3), 3.69 (m, 1), 5.2 (d, 1, J=5.9 Hz), 7.0–7.4 (m, 10). Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.10; H, 6.40; N, 5.82.

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