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Crystallization-induced asymmetric transformations and self-regeneration of stereocenters (SROSC): enantiospecific synthesis of α-benzylalanine and hydantoin BIRT-377

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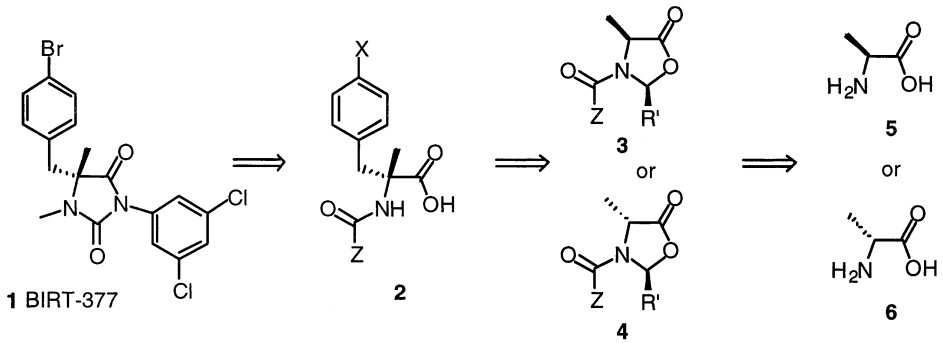
Abstract—*N*-Isobutoxycarbonyl protected L-alanine was condensed with 4-phenylbenzaldehyde in a crystallization-controlled process to give the corresponding *cis*-oxazolidinone derivative as the sole product in high yield; this underwent enolization and benzylation with the typical high degree of stereoselectivity observed in the SROSC involving this class of compounds.

Because of their important applications in medicinal chemistry, quaternary α-amino acids (and particularly methylated ones) have received much attention from the synthetic standpoint.[1] Among the many approaches to enantiomerically pure quaternary α-amino acids, the protocol called *Self-Regeneration of Stereocenters* (SROSC), devised and extensively studied by Seebach and co-workers, is especially attractive because it starts with natural amino acids (a class of compounds readily available in enantiomerically pure form), it does not employ any other chiral reagents or catalysts, and it enjoys a very broad generality.[2]

In the specific case of α-benzylalanines, such as the one (**2**, X = Br) we required for a large scale preparation of BIRT-377 (**1**, a hydantoin endowed with promising anti-inflammatory properties),[3] the embodiment of this principle would involve the benzylation of either the *cis* oxazolidinone **3** or its *trans* isomer **4**, resulting respectively from condensation of L-alanine (**5**) or its enantiomer (**6**) with an aldehyde and an acylating agent. Upon careful examination of the literature and some preliminary experiments, however, it becomes readily apparent that what may be hindering the general applicability of SROSC to large scale preparations of quaternary α-methylated amino acids is the rather awkward experimental protocol,[4] the risk of racemization upon condensation of the amino acid salt with an aldehyde, and the difficulty in producing either a *cis* or *trans* oxazolidinone (**3** or **4**) selectively. Apparently, no



Keywords: dynamic resolution; alkylation; quaternary amino acids; oxazolidinones; hydantoins.

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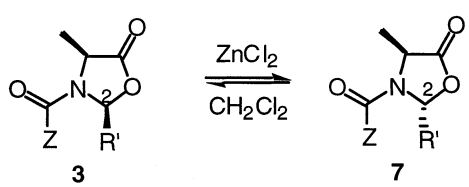
attempt has ever been made at understanding the mechanistic basis of the stereochemical outcome of C(2) in the step in which the oxazolidinone ring is formed, which is where the relay of chirality begins, and a recent review simply concludes that it is highly substituent-dependent.[1] As a matter of fact, depending on the nature of the aldehyde and the acylating agent, the Seebach protocol is reported to yield predominantly the *cis* isomer (4:1, R = *t*Bu, Z = Ph),[5] mostly *trans* (7.5:1, R = Z = Ph),[6] (2.5:1, R = Ph, Z = BnO),[7] exclusively *cis* (R = ferrocenyl, Z = *t*Bu),[8] and exclusively *trans* (R = Z = Ph).[9] We wish to report our approach to a rational and efficient solution of problems related to alkylation of alanine by means of the SROSC, which will hopefully make this method more suitable for large scale preparations of enantiomerically pure methylated quaternary α-amino acids.

We started by analyzing the thermodynamic profile of oxazolidinone formation, which was an easy task after finding that *N*-acylated-2-arylsubstituted derivatives undergo epimerization at the acetal position C(2) by exposure to a variety of acidic reagents (such as $ZnCl_2$ in methylene chloride, or trifluoroacetic acid, *p*-toluenesulfonic acid in refluxing benzene) to yield an equilibrium mixture of *cis* and *trans* isomers (**3** and **7**). Some equilibrium data illustrating the effect of the substituents are listed in Table 1. The *cis* isomer is generally favored; the *cis* isomer is more favored when the *N*-acyl substituent is an alkoxycarbonyl group rather than a benzoyl group (entries 1 and 2); the nature of the alkoxy group in the alkoxycarbonyl derivatives has little influence; a large aryl substituent at position 2 destabilizes the *cis* isomer.[10]

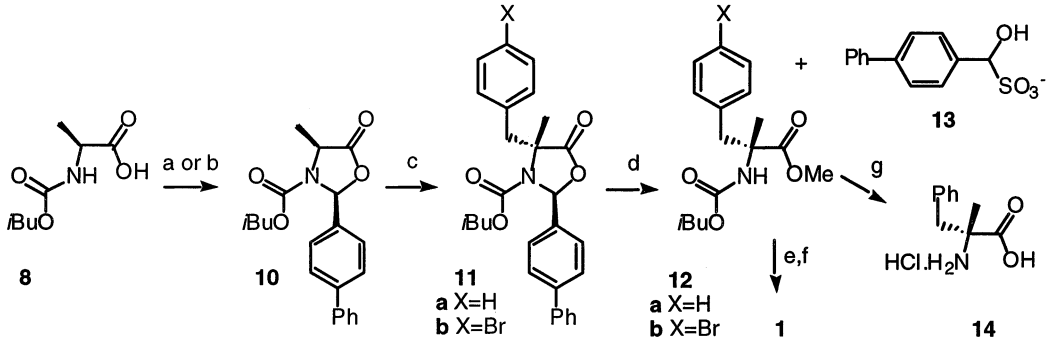
On the basis of the above observations, we decided that a suitable strategy to a single oxazolidinone could be the following: (a) improve the chemical synthesis of the oxazolidinone by maximizing the chemical yield and minimizing the risk of racemization, without concern for the stereochemical outcome and the ratio of isomers; (b) obtain one pure stereoisomeric oxazolidinone as a solid by devising a first or a second order asymmetric transformation.[11] We focused on *N*-alkoxycarbonyl-2-aryloxazolidinones, rather than *N*-acyl analogues because of their higher preference for the *cis* isomer and a possibly easier conversion to hydantoins. A derivative of suitable crystalline properties turned out to be **10**, for which two distinct highly efficient methods of synthesis (A and B) were devised.[12] According to method A, isobutoxycarbonyl alanine (**8**) was condensed with 4-phenylbenzaldehyde (**9**) under the typical conditions of acetal formation (reflux in a hydrocarbon solvent in the presence of *p*-toluenesulfonic acid under removal of water by azeotropic distillation);[13] an equilibrium mixture of **10** and its C(2) epimer resulted when a homogeneous solution was maintained throughout the reaction; but we were pleased to see that, when the condensation between **8** and **9** was carried out in the appropriate volume of cyclohexane or *iso*-octane, **10** precipitated as a nicely crystalline solid from the reaction mixture and could be isolated in 91% yield (with a negligible amount of its C(2) epimer in the mother liquors), thus demonstrating that oxazolidinone formation and its dynamic resolution could be very conveniently accomplished in the same step (Scheme 1). Alternatively, **8** was converted to the acid chloride (oxalyl chloride in methylene chloride) and this intermediate added to **9** in the presence of a catalytic amount of $ZnCl_2$;[14] an equilibrium mixture of **10** and its C(2) epimer resulted from the condensation of **8** and **9** in homogeneous solution: however, when most of the solvent of the reaction was removed and the product allowed to precipitate by addition of methyl *t*-butyl ether, pure **10** (88% yield) was isolated without precipitation of the epimer, which was present in the mother liquors in the thermodynamic proportions, thus showing that a second-order asymmetric transformation was operating under these conditions, as well. Method A was not suitable for condensation of **8** with 9-anthraldehyde. Both method A and B were not suitable for use with benzyloxycarbonyl-protected alanine.

With a very convenient approach to **10** in hand, we turned to the alkylation reaction. We found that **10** could be deprotonated with lithium hexamethyldisilazide and alkylated at a temperature of −27°C (much more convenient from an industrial standpoint than −78°C, as generally adopted in the alkylation step of SROSC) provided the base was added slowly to a mixture of nucleophile and electrophile. This gave **11** in excellent yield and high (>98%) diastereomeric purity. Much lower yields were obtained if the enolate was pre-formed at −27°C in the absence of the electrophile, suggesting that the lithium enolate of **10** is stable at −78°C, but not at −27°C. Treatment of **11** with lithium methoxide, followed by aqueous bisulfite work-up,[15] gave **12**, whereas 4-phenylbenzaldehyde precipitated as its bisulfite adduct **13** and could be filtered off. Crude **12a** was hydrolyzed to the free benzylated amino acid

Table 1. Equilibration of *cis* and *trans* oxazolidinones by C(2) epimerization (equilibration carried out with $ZnCl_2$ in CH_2Cl_2 at rt overnight; ratios by ^1H NMR)



Entry	Z	R^1	3:7
1	Ph	Ph	60:40
2	OMe	Ph	85:15
3	OMe	4'-biphenyl	85:15
4	O*i*Bu	Ph	85:15
5	O*i*Bu	4'-biphenyl	85:15
6	O*i*Bu	9-anthranyl	55:45



Scheme 1. (a) $(COCl)_2$ (cat. DMF) CH_2Cl_2, then 4-phenylbenzaldehyde (**9**) and $ZnCl_2$, 82%; (b) *p*-TsOH, cyclohexane reflux ($-H_2O$), 91%; (c) 4-bromobenzyl bromide or benzyl bromide, $LiN(SiMe_3)_2$, THF/hexane, −27°C, 100%; (d) MeOLi, MeOH, then saturated aqueous $NaHSO_3$, 97%; (e) 3,5-dichloroaniline, NaOMe, refluxing toluene, 64%; (f) MeI, NaOH, TBA–HSO_4, 95%; (g) HCl H_2O/AcOH, 100°C, 100%.

14 (as the hydrochloride) identical with an authentic sample. Also, the protected aminoacid esters **12** turned out to be excellent precursors to hydantoins; **12b** was in fact converted to **1** by treatment with the sodium derivative of 3,5-dichloroaniline (obtained in situ from the reaction of the aniline and sodium methoxide) in refluxing toluene,[16] followed by *N*-methylation; this approach to **1** (which includes only 5 steps from readily available **8**, has a 40% overall yield and >99.9% stereoselectivity) competes favorably with the previously reported ones.[3b]

In conclusion, a crystallization-induced process was devised by which L-alanine was converted to the *cis* oxazolidinone **10** (virtually free from its *trans* isomer) suitable as an intermediate for benzylation of alanine via the SROSC approach; the possibility of conducting the alkylation of **10** at −27°C rather than at −78°C was demonstrated; these findings should allow the application of SROSC to large scale preparation of alkylated alanines. Also, a new convenient entry to biologically important hydantoins is disclosed.

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4. We found the Na salt of alanine to be very hygroscopic and prone to forming a thick oil. Its conversion to the Schiff base under heterogeneous conditions in pentane, or higher hydrocarbons, was plagued by very long reaction times and erratic results. Acylation gave products with highly variable *cis*:*trans* ratios. Alternative condensation protocols: (a) Cheng, H.; Keitz, P.; Jones, J. B. *J. Org. Chem.* **1994**, *59*, 7671; (b) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337; (c) Zydowski, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. These approaches gave low yields when applied to our system. See also Ref. 1.
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10. These data can be rationalized if one considers, as can be seen by simple MM2 calculation, that the relative stability of compounds **3** and **7** is not primarily controlled by the direct interaction of substituents at C(2) and C(4) but by their interaction with the *N*-acyl substituent which tends to be coplanar with all the carbon atoms bound to the nitrogen. When the two substituents are *cis* to each other, their steric repulsion with the *N*-acyl substituent is readily minimized by a slight bending of the cycle; when the two substituents are *trans*, such a possibility for minimizing the steric repulsion is not effective. Only when the aryl substituent at C(2) is especially large (Table 1, entry 6), does the direct interaction with the substituent at C(4) become significant and the *cis* isomer is somewhat destabilized.
11. (a) Jacques, J.; Colbert, A. *Enantiomers, Racemates and Resolutions*; Wiley-Interscience: New York, 1981; (b) See also: Eliel, E. *Stereochemistry of Carbon Compounds*; MacGraw Hill: New York, 1994; (c) For a recent review of dynamic resolutions, see: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447.
12. Oxazolidinone **10**: *Method A*. The protected aminoacid **3** (10 g, 53 mmol), 4-phenylbenzaldehyde (10 g, 55 mmol) and *p*-toluenesulfonic acid (0.6 g) were heated to a rapid reflux in cyclohexane (150 mL) with continuous removal of the water formed by means of a Dean–Stark trap. After 18 h, a tan crystalline precipitate was formed; if not, an authentic sample of **10** was added to induce crystallization and the reflux continued for 8 h to ensure equilibration. Heating was discontinued, the mixture was allowed to equilibrate slowly at room temperature and then cooled in an ice bath; the solid was collected by suction; trituration with methyl *tert*-butyl ether gave pure

10 (17 g, 91%) as off-white prisms. A sample was recrystallized from methanol: mp 154–155°C; ^{1}H NMR ($CDCl_3$) δ 7.65–7.35 (m, 9H), 6.70 (s, 1H), 4.50 (q, $J=7$ Hz, 1H), 3.93 (d, $J=6.5$ Hz, 2H), 1.91 (m, 1H), 1.63 (d, $J=7$ Hz, 3H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.23, 154.36, 140.82, 136.49, 129.45, 128.33, 128.06, 127.74, 127.31, 89.59, 72.99, 52.75, 28.41, 19.53, 18.89. Anal. calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.30; H, 6.50; N, 3.82.

Method B. A solution of **8** (10 g, 52.8 mmol) and dimethyl formamide (0.5 mL) in dichloromethane (50 mL) was stirred at 10°C and oxalyl chloride (7 g, 4.8 mL, 55.2 mmol) was added over 15 min. The mixture was allowed to reach room temperature. After 1 h, 4-phenylbenzaldehyde (10 g, 54.9 mmol) was added in one portion, followed by anhydrous $ZnCl_2$ (0.50 g, 3.67 mmol). After a brief induction period, a mild exothermic reaction ensued and the solution turned from yellow to red. The solution was stirred for 4 h at rt while purging with a slow stream of nitrogen to remove the HCl formed. The solution was concentrated to about half of its volume, then methyl *t*-butylether (100 mL) was added and the slurry stirred at 4°C for 18 h. Filtration gave **10** as an off-white solid (16.5 g, 88%).

13. This quite obvious approach is not unprecedented (see Ref. 4b) but it has not found extensive application probably because of the poor results obtained with benzyloxycarbonyl protected alanine.
14. Although chlorides from *N*-alkoxycarbonyl amino acids are known to be configurationally stable in the presence of Lewis acids (Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972) and acid chlorides are known to give addition compounds with aldehydes (Neuenschwander, M.; Bigler, P.; Christen, K.; Iseli, R.; Kyburz, R.; Muehle, H. *Helv. Chim. Acta* **1978**, *61*, 2047) the combination of these reactions has never been used before in the preparation of enantiopure oxazolidinones.
15. For the regeneration of aldehydes from their bisulfite adducts, see: Kjell, D. P.; Slattery, B. J.; Semo, M. J. *J. Org. Chem.* **1999**, *64*, 5722.
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