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Intramolecular Ester Enolate–Imine Cyclization Reactions for the Asymmetric Synthesis of Polycyclic β-Lactams and Cyclic β-Amino Acid Derivatives

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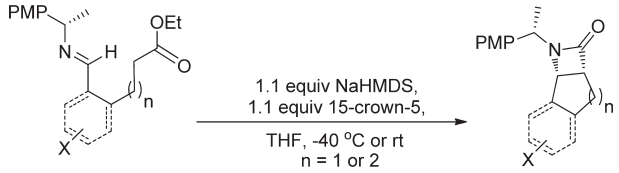
ABSTRACT



Enolates of chiral *N*-(α-methyl-*p*-methoxybenzyl)-ω-imino-esters undergo intramolecular cyclization reactions to afford (*syn*)-*aza*-anions of β-amino esters in high dr that cyclize to afford *N*-(α-methyl-*p*-methoxybenzyl)-β-lactams that can be readily deprotected to afford their corresponding cyclic *N*H-β-lactams, β-amino esters, or β-amino acids.

Chiral β-lactams exhibit a wide range of biological properties, including antibiotic, cholesterol absorption inhibition, antiviral, and protease inhibitor activities.[1] They are also used widely as versatile chiral building blocks for the synthesis of bioactive peptides, natural products, and heterocyclic drug molecules.[2] Popular methodologies for their asymmetric synthesis include Staudinger ketene–imine [2 + 2] cycloadditions, Kinugasa alkyne–nitrone cycloadditions, and intramolecular cyclization reactions of β-amino acid derivatives.[3] Stereoselective variants of ester enolate–imine condensation reactions have also been reported,[4] which rely on the addition of chiral ester enolate equivalents to achiral imines or addition of achiral ester enolate equivalents to chiral imines.[5] These *intermolecular* reactions arise from stereoselective addition of a metal enolate equivalent to an imine to afford the *aza*-anion of a chiral β-amino ester that then undergoes intramolecular ring closure onto its ester carbonyl to afford a monocyclic β-lactam. However, an *intramolecular* version of this type

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(1) (a) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072–5129. (b) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395–424. (c) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873–1887. (d) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Hache, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Deziel, R. *J. Med. Chem.* **1998**, *41*, 2882–2891. (e) Zhong, J. Y.; Groutas, W. C. *Curr. Top. Med. Chem.* **2004**, *4*, 1203–1216.

(2) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492.

(3) (a) Aranda, M. T.; Pérez-Faginas, P.; González-Muñiz, R. *Curr. Org. Synth.* **2009**, *6*, 325–341. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837–1872. (c) Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572–4573. (d) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198–2200. (e) Fenwick, D. R.; Davies, S. G. *J. Chem. Soc., Chem. Commun.* **1995**, 1109–1110.

(4) For reports of enantioselective ester enolate–imine cyclization reactions, see: (a) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715–716. (b) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219–11228. (c) Kambara, T.; Tomioka, K. *Chem. Pharm. Bull.* **2000**, *48*, 1577–1580.

(5) (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447–1465. (b) Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413–3416.

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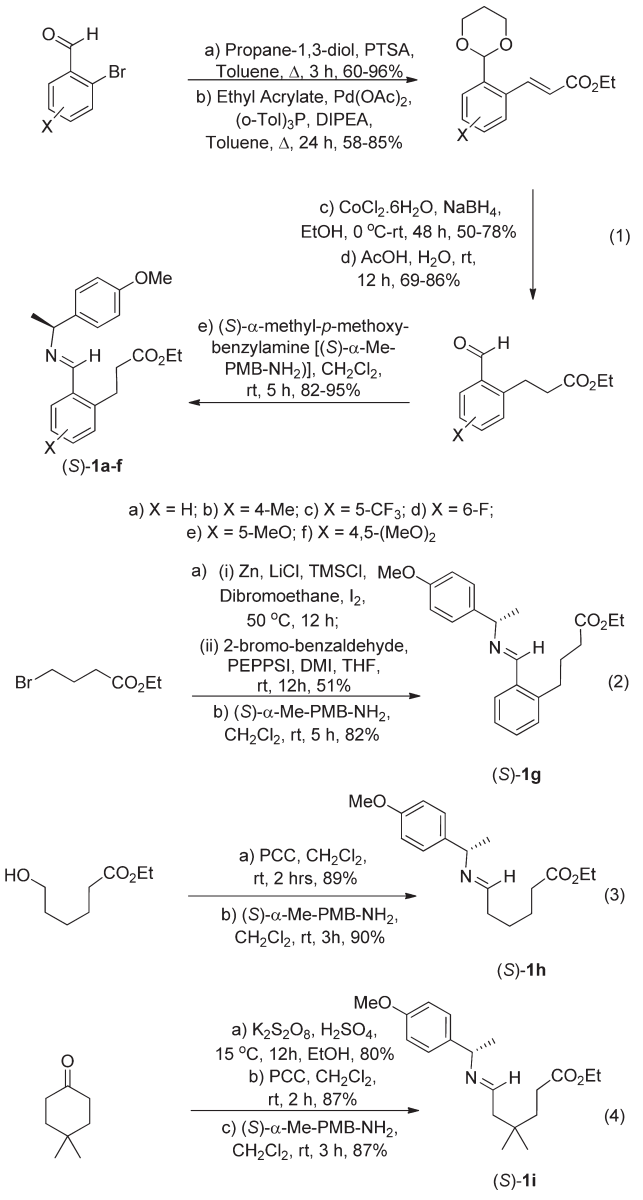
Scheme 1. Syntheses of ω-imino esters (*S*)-**1a**–**i**

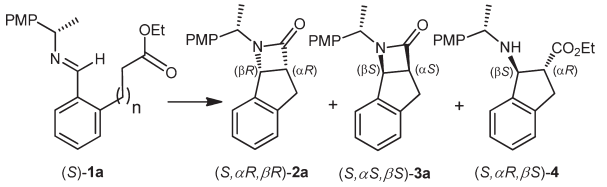


of ester enolate–imine cyclization reaction has not been reported to date, and we now report herein that enolates of chiral ω-imino esters can also undergo intramolecular cyclization reactions to afford polycyclic β-lactams with excellent levels of stereocontrol.

A series of cyclic and acyclic *N*-(α-methyl-*p*-methoxybenzyl)-ω-imino esters (*S*)-**1a**–**i** were prepared as potential cyclization substrates employing the range of synthetic protocols shown in Scheme 1. ω-Imino ester (*S*)-**1a** was chosen as a representative substrate for cyclization studies, and its enolate generated under a range of conditions.[6]

It was found that lithium or potassium enolates of (*S*)-**1a** in THF at room temperature underwent cyclization reactions to afford a mixture of β-lactam (*S*,α*R*,β*R*)-**2a**,[7,8] β-lactam (*S*,α*S*,β*S*)-**3a**, and (*anti*)-β-amino ester (*S*,α*R*,β*S*)-**4**[9] in moderate yields (Table 1, entries 1,2). The use of NaHMDS or KO^{t}Bu as bases in THF resulted in more selective reactions, affording a mixture of β-lactams **2a**/**3a** in 65:35 and 77:23 diastereoisomeric ratios (drs) respectively (Table 1, entries 3,4). Use of the noncoordinating solvent toluene did not result in any improvement in either the dr or yield of the reaction (Table 1, entry 5). However, the use of 1.1 equiv of NaHMDS and 15-crown-5 in THF gave β-lactam **2a** in a much improved 94:6 dr (Table 1, entry 6). Finally, it was found that using NaHMDS in THF at −40 °C, in the presence of 1.1 equiv of 15-crown-5, resulted in clean formation of tricyclic β-lactam **2a** in 99:1 dr in an isolated 82% yield (Table 1, entry 7).

Table 1. Optimization of Ester Enolate–Imine Cyclization Reactions of ω-Imino Ester (*S*)-**1a**



entry	conditions[a]	ratio of products[b] **2a**:**3a**:**4**
1	LiHMDS, THF, rt	**2a** (49):**3a** (18):**4** (33)
2	KHMDs, THF, rt	**2a** (30):**3a** (31):**4** (39)
3	KO^{t}Bu, THF, rt	**2a** (65):**3a** (35)
4	NaHMDS, THF, rt	**2a** (77):**3a** (23)
5	NaHMDS, Toluene, rt	**2a** (74):**3a** (26)
6	NaHMDS, THF, rt, 15-crown-5	**2a** (94):**3a** (6)
7	NaHMDS, THF, −40 °C, 15-crown-5	**2a** (99):**3a** (1)

[a] Use of sodium ethoxide, triethylamine, sodium hydride, or phosphazene as bases to generate enolates of (*S*)-**1a** did not afford any cyclization products. [b] Ratio of products determined from integration of respective peaks in the ^{1}H NMR spectra of crude reaction products.

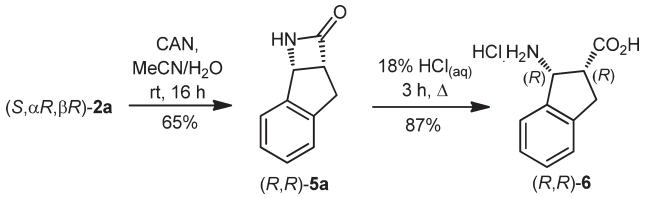
The absolute configuration of tricyclic β-lactam **2a** was confirmed as (*S*,α*R*,β*R*) *via* oxidative deprotection using ceric ammonium nitrate (CAN) to afford *N*H-β-lactam (*R*,*R*)-**5a**,[10] which was then hydrolyzed under acidic conditions to give the known β-amino acid (*R*,*R*)-**6** (Scheme 2).[11]

(6) For a previous report where 6-*endo*-trig cyclization of an ester enolate onto an imine was observed as the last step of a cascade reaction that gave a cyclic β-amino ester containing six vicinal stereocenters, see: Koutsaplis, M.; Andrews, P. C.; Bull, S. D.; Duggan, P. J.; Fraser, B. H.; Jensen, P. *Chem. Commun.* **2007**, 3580–3582.

(7) For previous asymmetric syntheses of benzocispentacin analogues see: (a) Fülöp, F.; Palkó, M.; Kámán, J.; Lázár, L.; Sillanpää, R. *Tetrahedron: Asymmetry* **2000**, *11*, 4179–4187. (b) Forró, E.; Fülöp, F. *Chem.—Eur. J.* **2006**, *12*, 2587–2592. (c) Price, D. A. *Synlett* **1999** 1919–1920. (d) Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *Liebigs Ann.* **1996**, 899–911.

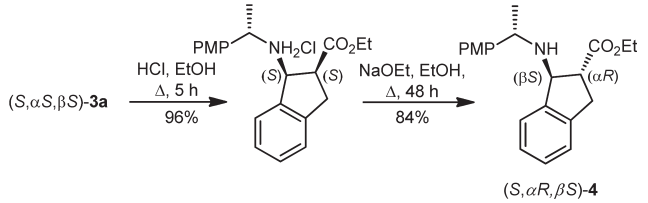
(8) For previous examples where intramolecular cyclization reactions of ester enolates onto imidoyl chlorides gave cyclic enamino esters that were stereoselectively hydrogenated to afford cyclic β-amino esters, see: Fustero, S.; Sánchez-Roselló, M.; Acenã, J. L.; Fernández, B.; Asensio, A.; Sanz-Cervera, J. F.; del Pozo, C. *J. Org. Chem.* **2009**, *74*, 3414–3423.

Scheme 2. Protocol Used To Assign the Configuration of β-Lactam (S,αR,βR)-**2a**



The five substituted ω-imino aryl esters (S)-**1b**–**f** were then treated with 1.1 equiv of NaHMDS in THF at −40 °C in the presence of 1.1 equiv of 15-crown-5 to give a range of tricyclic β-lactams (S,αR,βR)-**2b**–**f** in ≥95:5 dr in acceptable 59–79% isolated yields (Table 2, entries 1–5).[12] Reaction of the enolate of ω-imino ester (S)-**1g**, which contains an extra methylene unit in its ester side chain, under the same conditions, gave its corresponding tricyclic β-lactam (S,αR,βR)-**2g**, albeit in a reduced 92:8 dr (Table 2, entry 6). Cyclization of the acyclic enolates of ω-imino esters (S)-**1h**–**i** at room temperature also occurred in a highly stereoselective manner to give their corresponding bicyclic β-lactams (S,αR,βR)-**2h**–**i** in ≥96:4 dr (Table 2, entries 7–8).[13] The improved yield obtained for the formation of β-lactam **2i** over **2h** is likely to be due to the Thorpe–Ingold effect,[14] whereby the geminal dimethyl group of (S)-**1i** predisposes the conformation of its enolate toward intramolecular cyclization. Six of these β-lactams **2b**–**d** and **2g**–**i** were then oxidatively cleaved *via* treatment with CAN in CH_3CN/H_2O to afford their corresponding *N*H-β-lactams (R,R)-**5b**–**d,g** and (1S,2R)-**5h**–**i** (Figure 1).[15] β-Lactam (1S,2R)-**5h** could be converted into *cis*-pentacin ethyl ester (1S,2R)-**7** *via* treatment with acidic ethanol,

(9) The absolute configuration of the minor *anti*-β-amino-ester (S,αR,βS)-**4** was assigned *via* comparison of its spectroscopic data with an authentic sample prepared *via* sequential treatment of (S,αS,βS)-**3a** with HCl/EtOH and NaOEt in EtOH.



(10) Bull, S. D.; Davies, S. G.; Kelly, P. M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3106–3111.

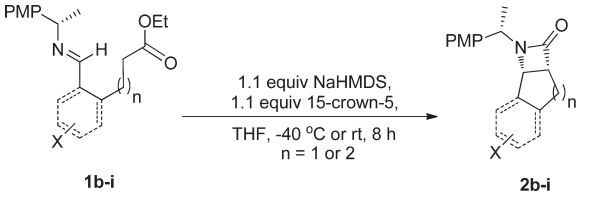
(11) (a) Schmitt, M. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2004**, *126*, 6848–6849. (b) Martinek, T. A.; Toth, G. K.; Vass, E.; Hollosi, M.; Fülöp, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 1718–1721. (c) Fülöp, F.; Forró, E.; Toth, G. K. *Org. Lett.* **2004**, *6*, 4239–4241. (d) Lengyel, G. A.; Frank, R. C.; Horne, W. S. *J. Am. Chem. Soc.* **2011**, *133*, 4246–4249.

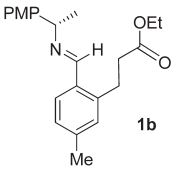
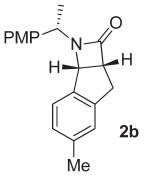
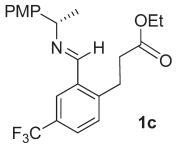
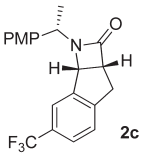
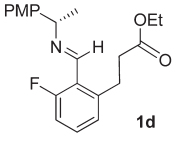
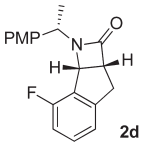
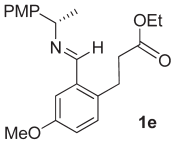
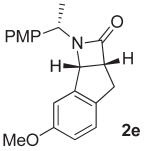
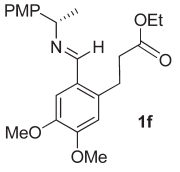
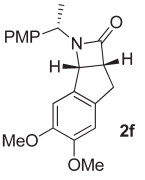
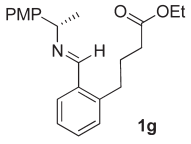
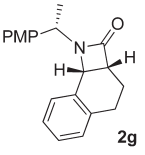
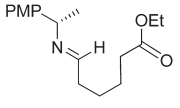
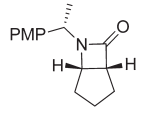
(12) The absolute configuration of trifluoro-aryl-β-lactam (αR,βR)-**2c** was confirmed by X-ray crystallographic analysis (see Supporting Information).

(13) Importantly, no cyclization products arising from competing formation of metalated enamine equivalents were observed in these reactions.

(14) For an excellent review on the factors affecting the steric promotion of ring formation, see: Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205–1222.

Table 2. Asymmetric Synthesis of (R,R)-β-Lactams **2b**–**i**



entry	substrate[a]	product	dr[b]	% yield
1	 **1b**	 **2b**	98:2	59
2	 **1c**	 **2c**	99:2	69
3	 **1d**	 **2d**	95:5	79
4	 **1e**	 **2e**	98:2	62
5	 **1f**	 **2f**	99:1	60
6	 **1g**	 **2g**	92:8	57
7	 **1h**	 **2h**	96:4	54
8	**1i**	**2i**	97:3	78

[a] Enolates of (S)-**1b**–**g** generated at −40 °C, while enolates of (S)-**1h**–**i** were generated at room temperature. [b] Drs determined from integration of respective peaks for **2b**–**i** in the ^{1}H NMR spectra of their crude reaction products.

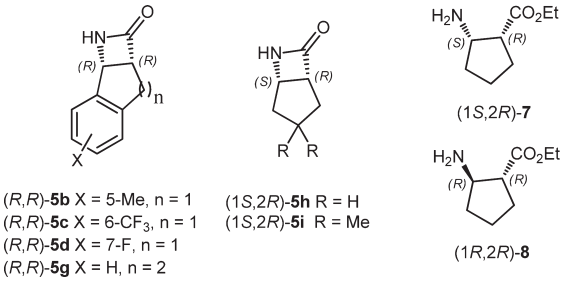
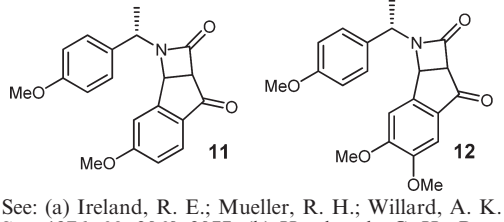


Figure 1. *N*H-β-lactams **5b**–**d,5g**–**i** and β-amino-esters **7** and **8**.

which in turn could be isomerized into *trans*-pentacin ethyl ester (1*R*,2*R*)-**8** *via* treatment with sodium ethoxide in refluxing *tert*-BuOH.[7]

The stereoselective outcome of these intramolecular ester enolate–imine cyclization reactions has been rationalized as follows. Literature precedent indicates that deprotonation of ester **1a** with NaHMDS in THF should afford a configurationally stable (*E*)-enolate **9** (Figure 2).[16] Since cyclization of the sodium enolate of ω-imino ester **1a** in the absence/presence of 15-crown-5 affords the same β-lactam **2a**, it is likely that its initial 5-*exo*-trig cyclization reaction proceeds *via* a nonchelated 'open' transition state.[17] As we have shown in our base catalyzed epimerization studies, (*anti*)-cyclic β-amino esters are thermodynamically more stable than their corresponding (*syn*)-diastereomers.[7] Therefore, it is proposed that an intramolecular cyclization reaction of (*E*)-**9** occurs under kinetic control to afford the *aza*-anion of (*syn*)-β-amino ester (*S*,α*R*,β*R*)-**10** (Figure 2).[18] This *aza*-anion **10** then undergoes rapid 4-*exo*-trig cyclization reaction onto the carbonyl of its ester group to give the observed β-lactam (*S*,α*R*,β*R*)-**2a** (Figure 2).[19]

(15) Attempts to oxidatively deprotect lactams **2e**–**f** using CAN afforded crude reaction products containing more than one product, the major components of which were the respective keto-β-lactams **11** and **12**. For a previous report of CAN mediated benzylic oxidation of Indane systems, see: Syper, L. *Tetrahedron Lett*. **1966**, *37*, 4493–4498.



(16) See: (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1976**, *98*, 2868–2877. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. A.; Sohn, J. E.; Lampe, J. *J. Org. Chem*. **1980**, *45*, 1066–1081.

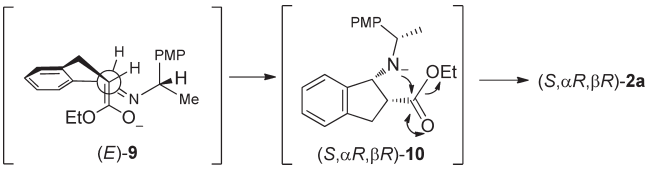


Figure 2. Mechanism of intramolecular ester enolate–imine cyclization reaction of (*S*)-**1a**.

In conclusion, we have shown that enolates of *N*-(α-methyl-*p*-methoxybenzyl)imino esters can undergo intramolecular cyclization reactions to afford (*syn*)-*aza*-anions that undergo 4-*exo*-trig cyclization reactions onto their ester carbonyl groups to afford cyclic β-lactams in high dr. These cyclic β-lactams may then be oxidatively deprotected to afford their corresponding *N*H-β-lactams, β-amino esters, or β-amino acids as required.[20] To the best of our knowledge, this report represents the first example of an intramolecular version of the ester enolate–imine condensation reaction, the first intermolecular variant of which was reported for the preparation of monocyclic β-lactams over 60 years ago.[21]

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Supporting Information Available. Experimental details, spectroscopic data, details of mechanistic experiments, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For selected reports where ester enolates undergo intermolecular cyclization reactions onto imines to afford (*syn*)-β-lactams, see: (a) Ha, D. C.; Hart, D. J.; Yang, T. K. *J. Am. Chem. Soc*. **1984**, *106*, 4819–4825. (b) Hart, D. J.; Lee, C. S.; Pirkle, W. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc*. **1986**, *108*, 6054–6056. (c) Braun, M.; Sacha, H.; Galle, D.; El-Alali, A. *Tetrahedron Lett*. **1995**, *36*, 4213–4216. (d) Ojima, I.; Habus, I. *Tetrahedron Lett*. **1990**, *31*, 4289–4292.

(18) We cannot discount the possibility that a reversible enolate–imine cyclization reaction is occurring to generate a diastereomeric mixture of (*anti*)-/(*syn*)-*aza*-anions under thermodynamic control. The equilibria of this reversible cyclization reaction could then be driven by the lowest energy (*syn*)-*aza*-anion (*S*,α*R*,β*R*)-**10** undergoing subsequent 4-*exo*-trig cyclization to afford (*S*,α*R*,β*R*)-β-lactam **2a**.

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