

Phosphoric Acid Catalyzed Desymmetrization of Bicyclic Bislactones Bearing an All-Carbon Stereogenic Center: Total Syntheses of (–)-Rhazinilam and (–)-Leucomidine B**

Jean-Baptiste Gualtierotti, Delphine Pasche, Qian Wang, and Jieping Zhu*

Abstract: In the presence of a catalytic amount of an imidodiphosphoric acid, enantioselective desymmetrization of bicyclic bislactones by reaction with alcohols took place smoothly to afford enantiomerically enriched monoacids having an all-carbon stereogenic center. Concise catalytic enantioselective syntheses of both (–)-rhazinilam and (–)-leucomidine B were subsequently developed using (S)-methyl 4-ethyl-4-formylpimelate monoacid as a common starting material.

Introduced by Kuehne in 1964,^[1] dimethyl 4-ethyl-4-formylpimelate (**1a**, R = Et; Figure 1) has been used as a key starting material in the syntheses of vincamine (**3**),^[1] 8-oxovincatine (**4**),^[2] vincadifformine (**5**),^[3] and other monoterpene indole alkaloids.^[4] However, the full potential of this prochiral ten-carbon synthon, an equivalent of a monoterpene

unit has, in our opinion, not been fully exploited. We assumed that prior to designing and to executing any synthetic plan using **1** as a key starting material, desymmetrization of this prochiral synthon to the enantioenriched monoacid **2** was a prerequisite. Previously, Amat, Bosch, et al. reported the desymmetrization of prochiral **1** to the piperidinone derivative **6** by cyclocondensation of **1** with a stoichiometric amount of (R)-phenylglycinol.^[5] However, rapid and enantioselective synthesis of **2a** (R = Et) remained to be developed.^[6] In connection with our ongoing projects focused on the synthesis of indole alkaloids,^[7] we became interested in desymmetrizing Kuehne's aldehyde and its subsequent application in natural product synthesis. We report herein that in the presence of a catalytic amount of chiral phosphoric acid,^[8,9] bicyclic bislactones derived from diesters **1** are readily desymmetrized to enantioenriched monoacids (**2**) having an all-carbon stereogenic center. We also document a unified and divergent synthesis of two structurally distinct monoterpene indole alkaloids, (–)-rhazinilam (**7**) and (–)-leucomidine B (**8**), using **2a** (R = Et) as a common starting material (Figure 1).

To the best of our knowledge, desymmetrization of dimethyl 4,4-disubstituted pimelate has never been reported. Our initial attempts to differentiate the two enantiotopic ester functions in **1** and the protected form **9** (Figure 2), using lipase

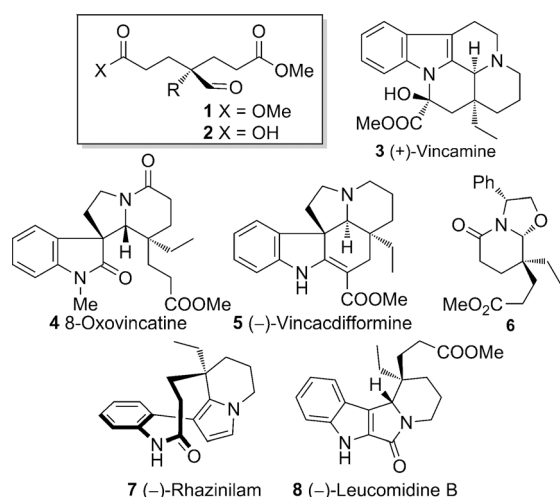


Figure 1. Kuehne's aldehyde and its use in natural product synthesis.

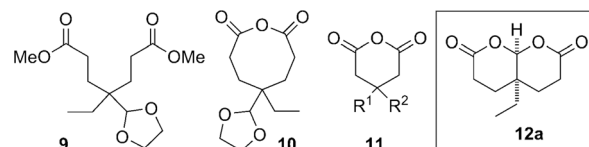


Figure 2. Desymmetrization of Kuehne's aldehyde and its derivatives.

and esterase, met with failure (see the Supporting Information).^[10] Attempts to desymmetrize the eight-membered cyclic anhydride **10** were equally unsuccessful. In the presence of various organocatalysts, including *Cinchona*-alkaloid derivatives^[11] and BINOL-derived chiral phosphoric acids,^[12,13] reaction of **10** with methanol at –20 °C was very slow, thus affording, after 48 h, the racemic monoacid **2a** (R = Et) in less than 20 % yield. These results are in sharp contrast to the facile desymmetrization of five- and six-membered *meso* or prochiral anhydrides such as **11** (Figure 2), thus indicating the challenges associated with the desymmetrization of **1**.

Considering other substrates derived from Kuehne's aldehyde, which are susceptible to desymmetrization, we turned our attention to the bicyclic bislactone **12a**. In analogy

[*] J.-B. Gualtierotti, D. Pasche, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: <http://lspn.epfl.ch>

[**] We thank EPFL (Switzerland), the Swiss National Science Foundation (SNSF), the Swiss National Centres of Competence in Research NCCR-Chemical Biology, the COST action (CM0905), and the Swiss State Secretariat for Education and Research for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201405842>.

to the anhydride **11**, which is an excellent substrate for desymmetrization, we hypothesized that **12a** could be similarly desymmetrized. The carbonyl carbon atoms in **12a** are certainly less electrophilic than those in **11**, nevertheless we assumed that the cascade fragmentation initiated by nucleophilic attack to one of the carbonyl groups in **12a** could provide a reasonable driving force to facilitate the occurrence of the desired transformation. Although it has scarcely been described in the literature,^[14] **12a** was easily synthesized from **1a** (NaOH, then Ac₂O) in 95% yield. The *cis* stereochemistry of the bicyclic ring system was determined by X-ray crystal structure analysis.^[15,16]

Initial experiments on the desymmetrization of **12a** using methanol (2.0 equiv) as a nucleophile in the presence of a chiral phosphoric acid (0.1 equiv; Figure 3) gave very promising results (Table 1, entries 1–5). Reaction of **12a** with MeOH (2.0 equiv) at room temperature in the presence of TRIP **13e** (0.1 equiv) afforded the monoacid **2a** in 95% yield with an e.r. of 84:16 (entry 5). Interestingly, decreasing

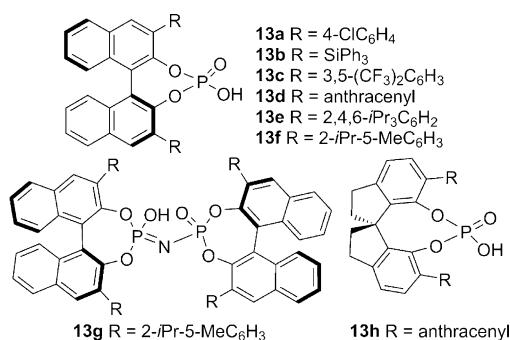


Figure 3. Structure of chiral phosphoric acids derived from (*S*)-BINOL and (*S*)-SPINOL.

Table 1: Desymmetrization of bicyclic bislactone **12a**: Survey of catalytic conditions.

Entry	Cat.	Solvent	<i>T</i> [°C]	e.r. ^[b]
1	13a	toluene	RT	55:45
2	13b	toluene	RT	65:35
3	13c	toluene	RT	65:35
4	13d	toluene	RT	80:20
5	13e	toluene	RT	84:16
6	13e	toluene	−10	75:25
7	13e	toluene	−60	55:45
8	13e	MeCN	RT	86:14
9	13e	THF	RT	88:12
10	13e	1,4-dioxane	RT	89:11
11	13e	TBME	RT	85:15
12	13f	1,4-dioxane	RT	80:20
13	13g	1,4-dioxane	RT	92:8
14	13h	1,4-dioxane	RT	92:8

[a] All reactions were run at 0.1 mmol scale at RT, methanol (2.0 equiv), catalyst (0.1 equiv), *c* 0.1 M. [b] e.r. was determined by SFC analysis on a chiral stationary phase (see the Supporting Information for full details). TBME = *tert*-butyl methyl ether, THF = tetrahydrofuran.

the reaction temperature under otherwise identical reaction conditions produced the monoacid with reduced enantioselectivities (entries 5–7). Among the different solvents examined (entries 8–11), 1,4-dioxane turned out to be the solvent of choice (entry 10). An additional increase in the enantioselectivity was observed with **13g**^[17] and **13h** (entries 13 and 14).^[18] Since we found that the imidodiphosphoric acid **13g**, reported by List and co-workers, was more easily recovered from the reaction mixture than **13h** (STRIP), it was chosen for examining the scope of this novel desymmetrization process. The 4*S* absolute configuration of **2a** was determined by X-ray crystal structure analysis of the corresponding 4-(4'-bromophenyl)phenyl ester of **2a**.^[19]

As shown in Table 2, in addition to methanol (entry 1), benzyl alcohol (entry 2) and isopropyl alcohol (entry 3) can also act as nucleophiles to enantioselectively open **12**, with benzyl alcohol giving a slightly better result. The presence of

Table 2: Scope of the desymmetrization.

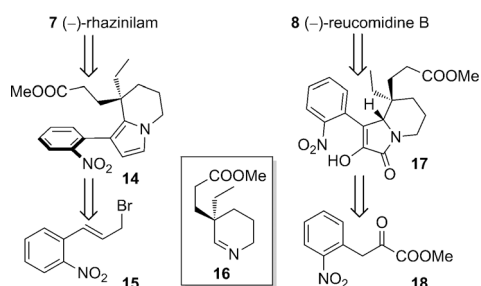
Entry	R ¹	R ²	R ³	Product	Yield [%]	e.r. ^[b]
1	H	Et	Me	2a	95	92:8
2	H	Et	Bn	2b	80	95:3:4.7
3	H	Et	<i>i</i> Pr	2c	75	91:7:8.3
4	H	vinyl	Me	2d	94	91:9
5	H	allyl	Me	2e	95	91:2:8.8
6	H	<i>i</i> Pr	Me	2f	82	92.5:7.5
7	H	Ph	Me	2g	90	96.3:3.7
8	H	CH ₂ CH ₂ SPh	Me	2h	91	93.2:6.8
9	H	CH ₂ CH ₂ CH ₂ OBn	Me	2i	95	94.7:5.3
10	Ph	Me	Me	2j	66	90.7:9.3

[a] All reactions were performed on a 0.1 mmol scale, R³OH (2.0 equiv), **13g** (0.1 equiv) in 1,4-dioxane (*c* 0.1 M), RT. [b] Determined by SFC analysis on a chiral stationary phase (see the Supporting Information for full details).

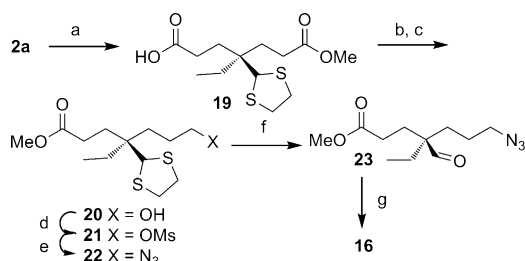
substituents such as vinyl, allyl, isopropyl, phenyl 2-(thiophenoxy)ethyl, and 3-(benzyloxy)propyl at the C4a-position was well tolerated, thus affording, after methanolysis, the corresponding enantiomerically enriched aldehydes **2d–i** (entries 4–9) and ketone **2j** (entry 10) in good to excellent yields and enantioselectivities.

Total syntheses of (−)-rhazinilam (**7**)^[20,21] and (−)-leucomidine B (**8**)^[22] were next envisaged using **2a** as a starting material. Retrosynthetically, **7** can be prepared from **14** by a reduction and macrolactamization sequence (Scheme 1). The tetrahydroindolizine **14** could in turn be obtained by a formal [3+2] cycloaddition between the allylbromide **15** and tetrahydropyridine (*R*)-**16**.^[21b,c] Likewise, (−)-leucomidine B (**8**) could be accessed by a facile indolization of **17** which was in turn thought to be accessible by condensation of (*R*)-**16** with the α-ketoester **18**.

The synthesis of (*R*)-**16**, a common starting material to both natural products, is shown in Scheme 2. Protection of the aldehyde in **2a** was found to be more difficult than it might appear. After a number of unsuccessful trials, the aldehyde



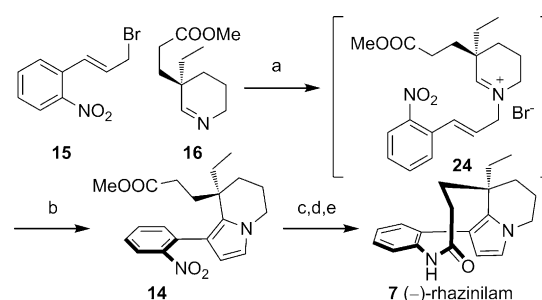
Scheme 1. Retrosynthetic analysis of (–)-rhazinilam (**7**) and (–)-leucomidine B (**8**).



Scheme 2. Synthesis of the tetrahydropyridine **16**. a) Ethanedithiol, Hf(OTf)₄, (0.05 equiv), CH₂Cl₂, 95%; b) LiBH₄, THF; c) TMSCHN₂, MeOH, 95% for two steps; d) MsCl, NEt₃, CH₂Cl₂; e) NaN₃ (2.0 equiv), DMF, 50°C, 83% for two steps; f) IBX, TBAB, AcOH/DMSO/H₂O (1:8:1); g) PPh₃, THF/H₂O (9:1), 60% for two steps. DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, IBX = *o*-iodoxybenzoic acid, Ms = methanesulfonyl, TBAB = tetra-*n*-butylammoniumfluoride, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

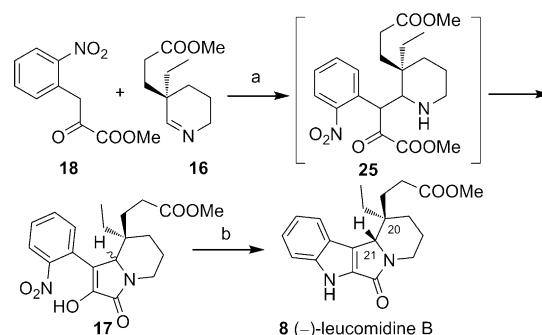
was converted into the 1,3-dithiolane **19** in 95% yield.^[23] Chemoselective reduction of the ester to the alcohol (LiBH₄) and subsequent esterification of the carboxylic acid afforded **20**. The primary alcohol was subsequently transformed into the azide **22** via the mesylate intermediate **21**. Deprotection of the dithiolane was realized using a modified literature procedure (IBX, TBAB, AcOH, DMSO/H₂O) to afford the azido aldehyde **23**.^[24] Staudinger reduction of the azide and subsequent intramolecular aza-Wittig reaction converted **23** into the cyclic imine **16** in 60% yield. By using BH₃ instead of LiBH₄ for the chemoselective reduction of the acid function, the compound **19** was converted into *ent*-**16** following exactly the same synthetic sequence.

The total synthesis of (–)-rhazinilam (**7**) was accomplished as shown in Scheme 3. Heating a DMF solution of **15** and (*R*)-**16** afforded the iminium salt **24**, which upon heating in toluene in the presence of freshly prepared Ag₂CO₃ (2.0 equiv) furnished **14** in 60% overall yield.^[21b,c,25] The compound **14** turned out to be air sensitive, therefore, the oxidative annulation had to be performed under a strictly inert atmosphere. Hydrogenation of the nitro group to give the amine, and subsequent saponification and lactamization provided **7** in 80% overall yield. The synthetic **7** displayed physical and spectroscopic data identical in all respects to those reported for the natural product.



Scheme 3. Total synthesis of (–)-rhazinilam (**7**). a) DMF, 100°C; b) Ag₂CO₃, toluene, 110°C, 1 h, 60% for two steps; c) Pd/C, H₂, MeOH; d) KOH, MeOH/H₂O (1:1); e) EDC, DMAP, NEt₃, CH₂Cl₂, 80% for three steps. DMAP = 4-(*N,N*-dimethyl)pyridine, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

A total synthesis of (–)-leucomidine B (**8**), isolated in 2012 by Morita,^[22] has not been reported. Our synthesis started by condensation of methyl 3-(2-nitrophenyl)-2-oxopropanoate (**18**)^[26] with (*R*)-**16**. Simply heating (*R*)-**16** and **18** afforded the [3+2] annulation product **17** as a mixture of two diastereomers (d.r. = 1:1) in 70% yield (Scheme 4). The



Scheme 4. Total synthesis of (–)-leucomidine B (**8**). a) Toluene, 90°C, 80%; b) Pd/C, H₂, then toluene, 110°C, 40% of **8** + 40% of its C21 epimer (d.r. = 1:1).

reaction was most probably initiated by the intermolecular Mannich reaction and subsequent intramolecular transamidation of the resulting Mannich adduct **25**. The compound **17** existed exclusively as the enol form. However, the ¹H NMR spectra of the two purified diastereomers are more complicated than expected because of the presence of atropisomers around the C(sp²)–C(sp²) bond. Hydrogenation of **17** followed by heating a toluene solution of the crude aniline afforded **8** and its C21 epimer in 80% overall yield (d.r. = 1:1). The two epimers were readily separable and one of the diastereomers displayed physical and spectroscopic data identical in all respects to those reported for **8**^[27] [Synthetic: [α]_D –18.6 (c 0.3, CHCl₃); natural: [α]_D –18 (c 0.3, CHCl₃)]. We have also synthesized (+)-leucomidine B (*ent*-**8**) from *ent*-**16** by using exactly the same synthetic scheme {[α]_D +14.3 (c 0.3, CHCl₃)}. Therefore, the 20*R*,21*S* absolute configuration of **8**, initially assigned based on detailed NMR and CD spectra studies, was confirmed by the present total synthesis.

In summary, we developed a new strategy for the desymmetrization of prochiral diesters **1** via the bicyclic bislactone surrogates **12**. In the presence of the chiral imidodiphosphoric acid **13g**, desymmetrization of the bislactones **12** with an alcohol took place smoothly to afford the enantiomerically enriched 4-substituted-4-formylpimelate monoacids **2** in good to excellent yields and good enantioselectivities. The utility of **2** as chiral building blocks in natural products synthesis was illustrated by the development of a concise total synthesis of (–)-razinilam (**7**) and the first total synthesis of (–)-leucomidine (**8**).

Received: June 2, 2014

Revised: June 24, 2014

Published online: July 22, 2014

Keywords: alkaloids · natural products · organocatalysis · synthetic methods · total synthesis

- [1] M. E. Kuehne, *J. Am. Chem. Soc.* **1964**, *86*, 2946.
- [2] L. Castedo, J. Harley-Mason, M. Kaplan, *J. Chem. Soc. D* **1969**, 1444.
- [3] a) J.-Y. Laronze, J. Laronze-Fontaine, J. Lévy, J. Le Men, *Tetrahedron Lett.* **1974**, *15*, 491; b) A. Nemes, C. Szántay, Jr., L. Czibula, I. Greiner, *ARKIVOC* **2008**, 154.
- [4] *Aspidosperma* family, see: a) G. Costello, J. E. Saxton, *Tetrahedron* **1986**, *42*, 6047; b) J. W. Blowers, J. E. Saxton, A. G. Swanson, *Tetrahedron* **1986**, *42*, 6071; Attempted synthesis of rhazinilam, see: c) C. Carité, J. P. Alazard, K. Ogino, C. Thal, *Tetrahedron Lett.* **1990**, *31*, 7011; d) J.-P. Alazard, C. Terrier, A. Mary, C. Thal, *Tetrahedron* **1994**, *50*, 6287.
- [5] a) M. Amat, M. Cantó, N. Llor, V. Ponzo, M. Pérez, J. Bosch, *Angew. Chem.* **2002**, *114*, 345; *Angew. Chem. Int. Ed.* **2002**, *41*, 335; b) M. Amat, O. Bassas, N. Llor, M. Cantó, M. Pérez, E. Molins, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 7872.
- [6] J. C. F. Alves, A. B. C. Simas, P. R. R. Costa, J. D'Angelo, *Tetrahedron: Asymmetry* **1997**, *8*, 1963.
- [7] a) T. Gerfaud, C. Xie, L. Neuville, J. Zhu, *Angew. Chem.* **2011**, *123*, 4040; *Angew. Chem. Int. Ed.* **2011**, *50*, 3954; b) T. Buyck, Q. Wang, J. Zhu, *Org. Lett.* **2012**, *14*, 1338; c) T. Buyck, Q. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 12946; *Angew. Chem. Int. Ed.* **2013**, *52*, 12714; d) Z. Xu, Q. Wang, J. Zhu, *Angew. Chem.* **2013**, *125*, 3354; *Angew. Chem. Int. Ed.* **2013**, *52*, 3272; e) Z. Xu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 19127; f) W. Ren, Q. Wang, J. Zhu, *Angew. Chem.* **2014**, *126*, 1849; *Angew. Chem. Int. Ed.* **2014**, *53*, 1818.
- [8] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804.
- [9] a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; b) M. Terada, *Chem. Commun.* **2008**, 4097; c) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 395; d) M. Terada, *Curr. Org. Chem.* **2011**, *15*, 2227; e) M. Rueping, A. Kuenkel, I. Atodiressei, *Chem. Soc. Rev.* **2011**, *40*, 4539; f) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498.
- [10] E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2005**, *105*, 313.
- [11] a) Y. Chen, P. McDavid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965; b) L. Atodiressei, I. Schiffrs, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683.
- [12] Chiral phosphoric acid-catalyzed desymmetrization, see: a) S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem.* **2008**, *120*, 2882; *Angew. Chem. Int. Ed.* **2008**, *47*, 2840; b) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084; c) K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem.* **2009**, *121*, 9832; *Angew. Chem. Int. Ed.* **2009**, *48*, 9652; d) Q.-W. Zhang, C.-A. Fan, H.-J. Zhang, Y.-Q. Tu, Y.-M. Zhao, P. Gu, Z.-M. Chen, *Angew. Chem.* **2009**, *121*, 8724; *Angew. Chem. Int. Ed.* **2009**, *48*, 8572; e) G. D. Sala, A. Lattanzi, *Org. Lett.* **2009**, *11*, 3330; f) V. N. Wakchaure, B. List, *Angew. Chem.* **2010**, *122*, 4230; *Angew. Chem. Int. Ed.* **2010**, *49*, 4136; g) Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 4056; h) L. Ren, T. Lei, L.-Z. Gong, *Chem. Commun.* **2011**, *47*, 11683; i) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.* **2011**, *133*, 18534; j) M. Yang, Y.-M. Zhao, S.-Y. Zhang, Y.-Q. Tu, F.-M. Zhang, *Chem. Asian J.* **2011**, *6*, 1344; k) D. M. Rubush, M. A. Morges, B. J. Rose, D. H. Thamm, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 13554; l) K. Mori, Y. Ichikawa, M. Kobayashi, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 3964; m) Z. Wang, Z. Chen, J. Sun, *Angew. Chem.* **2013**, *125*, 6817; *Angew. Chem. Int. Ed.* **2013**, *52*, 6685; n) Z. Chen, J. Sun, *Angew. Chem.* **2013**, *125*, 13838; *Angew. Chem. Int. Ed.* **2013**, *52*, 13593; o) G. Qabaja, J. E. Wilent, A. R. Benavides, G. E. Bullard, K. S. Petersen, *Org. Lett.* **2013**, *15*, 1266; p) A. D. Lackner, A. V. Samant, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14090; metal/phosphoric acid catalyzed desymmetrization: q) Z. Chai, T. J. Rainey, *J. Am. Chem. Soc.* **2012**, *134*, 3615; r) B. Guo, G. Schwarzwald, J. T. Njardarson, *Angew. Chem.* **2012**, *124*, 5773; *Angew. Chem. Int. Ed.* **2012**, *51*, 5675; s) A. K. Mourad, J. Leutzow, C. Czekelius, *Angew. Chem.* **2012**, *124*, 11311; *Angew. Chem. Int. Ed.* **2012**, *51*, 11149.
- [13] For other recent examples of chiral phosphoric acid catalyzed kinetic resolution/dynamic kinetic resolution, see: a) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He, S.-L. You, *Eur. J. Org. Chem.* **2010**, *47*; b) M. Rueping, U. Urias, M.-Y. Lin, I. Atodiressei, *J. Am. Chem. Soc.* **2011**, *133*, 3732; c) C. Wang, H.-W. Luo, L.-Z. Gong, *Synlett* **2011**, 992; d) G. Lu, V. B. Birman, *Org. Lett.* **2011**, *13*, 356; e) M. Yamanaka, M. Hoshino, T. Katoh, K. Mori, T. Akiyama, *Eur. J. Org. Chem.* **2012**, 4508; f) X.-S. Wu, S.-K. Tian, *Chem. Commun.* **2012**, *48*, 898; g) I. Čorić, J. H. Kim, T. Vlaar, M. Patil, W. Thiel, B. List, *Angew. Chem.* **2013**, *125*, 3574; *Angew. Chem. Int. Ed.* **2013**, *52*, 3490; h) S. Harada, S. Kuwano, Y. Yamaoka, K.-I. Yamada, K. Takasu, *Angew. Chem.* **2013**, *125*, 10417; *Angew. Chem. Int. Ed.* **2013**, *52*, 10227; i) K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740; silver phosphate catalyzed: j) Y. Wang, K. Zheng, R. Hong, *J. Am. Chem. Soc.* **2012**, *134*, 4096.
- [14] R. Chong, P. S. Clezy, *Aust. J. Chem.* **1967**, *20*, 123.
- [15] CCDC 1002333 (**12a**) contains 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.
- [16] The structure of the bislactone **12a** in the solid state did not possess an obvious plane of symmetry. However, we use the term desymmetrization in this paper for the sake of convenience.
- [17] a) I. Čorić, B. List, *Nature* **2012**, *483*, 315; b) S. Liao, I. Čorić, Q. Wang, B. List, *J. Am. Chem. Soc.* **2012**, *134*, 10765; c) J. H. Kim, I. Čorić, S. Vellalath, B. List, *Angew. Chem.* **2013**, *125*, 4570; *Angew. Chem. Int. Ed.* **2013**, *52*, 4474.
- [18] a) I. Čorić, S. Müller, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 17370; b) F. Xu, D. Huang, C. Han, W. Shen, X. Lin, Y. Wang, *J. Org. Chem.* **2010**, *75*, 8677.
- [19] The quality of the monocrystal was not good enough to create a cif file. However, the so generated structure (see the Supporting Information) allowed us to determine without ambiguity the absolute configuration of **2a**.
- [20] Isolation: a) D. J. Abraham, R. D. Rosenstein, R. L. Lyon, H. H. S. Fong, *Tetrahedron Lett.* **1972**, *13*, 909; b) K. T. De Silva, A. H. Ratcliffe, G. F. Smith, G. N. Smith, *Tetrahedron Lett.* **1972**,

- 13, 913; c) for a review, see: O. Baudoin, D. Guénard, F. Guéritte, *Mini-rev. Org. Chem.* **2004**, *1*, 333.
- [21] For total synthesis of (±)-rhazinilam, see: a) A. H. Ratcliffe, G. F. Smith, G. N. Smith, *Tetrahedron Lett.* **1973**, *14*, 5179; b) J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2000**, *122*, 6321; c) P. Magnus, T. Rainey, *Tetrahedron* **2001**, *57*, 8647; d) A. L. Bowie, Jr., C. C. Hughes, D. Trauner, *Org. Lett.* **2005**, *7*, 5207; e) L. McMurray, E. M. Beck, M. J. Gaunt, *Angew. Chem.* **2012**, *124*, 9422; *Angew. Chem. Int. Ed.* **2012**, *51*, 9288; f) X. Sui, R. Zhu, G. Li, X. Ma, Z. Gu, *J. Am. Chem. Soc.* **2013**, *135*, 9318; for synthesis of (–)-rhazinilam, see: g) J. A. Johnson, N. Li, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 6900; h) Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 10352; i) M. G. Banwell, D. A. S. Beck, A. C. Willis, *ARKIVOC* **2006**, 163; j) Z. Gu, A. Zakarian, *Org. Lett.* **2010**, *12*, 4224; k) K. Sugimoto, K. Toyoshima, S. Nonaka, K. Kotaki, H. Ueda, H. Tokuyama, *Angew. Chem.* **2013**, *125*, 7309; *Angew. Chem. Int. Ed.* **2013**, *52*, 7168.
- [22] M. Motegi, A. E. Nugroho, Y. Hirasawa, T. Arai, A. H. A. Hadi, H. Morita, *Tetrahedron Lett.* **2012**, *53*, 1227.
- [23] Y.-C. Wu, J. Zhu, *J. Org. Chem.* **2008**, *73*, 9522.
- [24] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4211; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077.
- [25] R. Grigg, P. Myers, A. Somasunderam, V. Sridharan, *Tetrahedron* **1992**, *48*, 9735.
- [26] K. C. Nicolaou, A. A. Estrada, G. C. Freestone, S. H. Lee, X. Alvarez-Mico, *Tetrahedron* **2007**, *63*, 6088.
- [27] Purification by semipreparative SFC on a chiral OD-H column afforded enantiopure leucomidine B.