Organocatalysis

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

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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 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

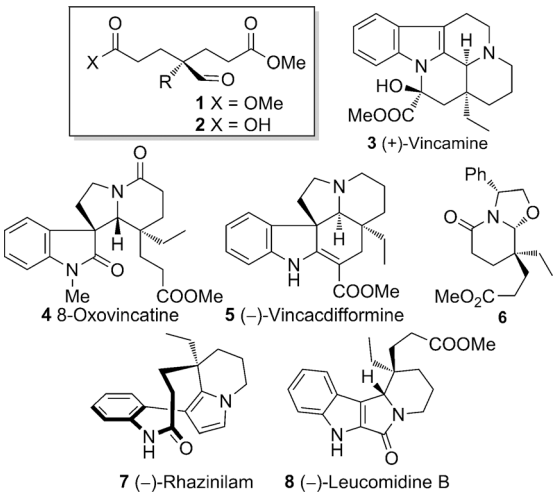

Figure 1. Kuehne's aldehyde and its use in natural product synthesis.

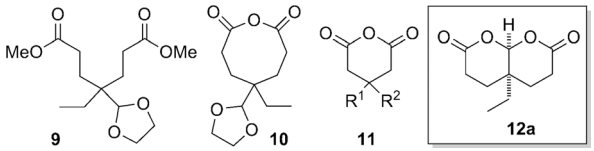

Figure 2. Desymmetrization of Kuehne's aldehyde and its derivatives.

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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 Ac_2O) 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

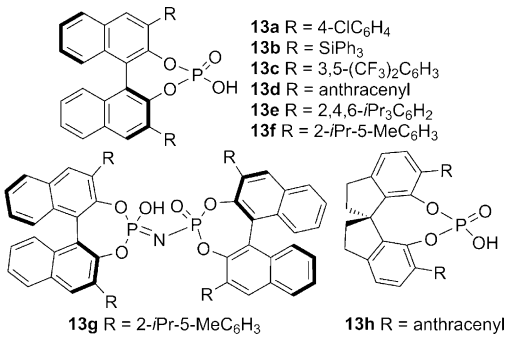
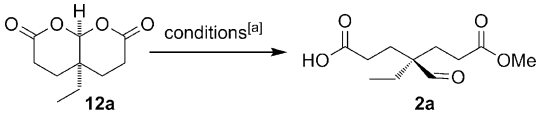


Figure 3. Structure of chiral phosphoric acids derived from (*S*)-BINOL and (*S*)-SPINOL.

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



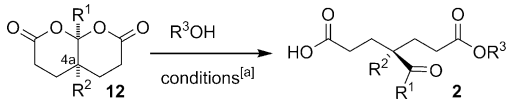
Entry	Cat.	Solvent	*T* [°C]	e.r.[b]
1	**13a**	toluene	RT	55:45
2	**13b**	toluene	RT	65:35
3	**13c**	toluene	RT	65:35
4	**13d**	toluene	RT	80:20
5	**13e**	toluene	RT	84:16
6	**13e**	toluene	−10	75:25
7	**13e**	toluene	−60	55:45
8	**13e**	MeCN	RT	86:14
9	**13e**	THF	RT	88:12
10	**13e**	1,4-dioxane	RT	89:11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



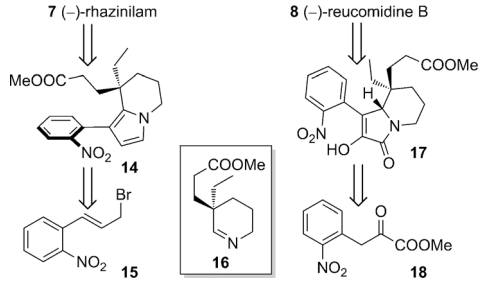
Entry	R^1	R^2	R^3	Product	Yield [%]	e.r.[b]
1	H	Et	Me	**2a**	95	92:8
2	H	Et	Bn	**2b**	80	95.3:4.7
3	H	Et	*i*Pr	**2c**	75	91.7:8.3
4	H	vinyl	Me	**2d**	94	91:9
5	H	allyl	Me	**2e**	95	91.2:8.8
6	H	*i*Pr	Me	**2f**	82	92.5:7.5
7	H	Ph	Me	**2g**	90	96.3:3.7
8	H	CH_2CH_2SPh	Me	**2h**	91	93.2:6.8
9	H	$CH_2CH_2CH_2OBn$	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, R^3OH (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).

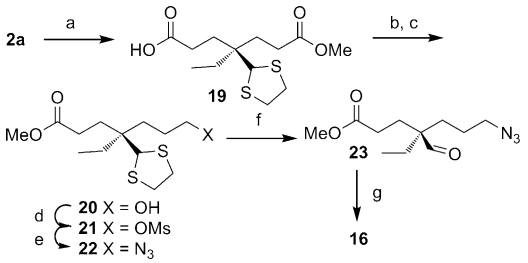
substituents such as vinyl, allyl, isopropyl, phenyl 2-(thiophenoxy)ethyl, and 3-(benzyloxy)propyl at the C4a-position was well tolerated, thus affording, after methanolysis, the corresponding enantiomerically enriched aldehydes **2d**–**i** (entries 4–9) and ketone **2j** (entry 10) in good to excellent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



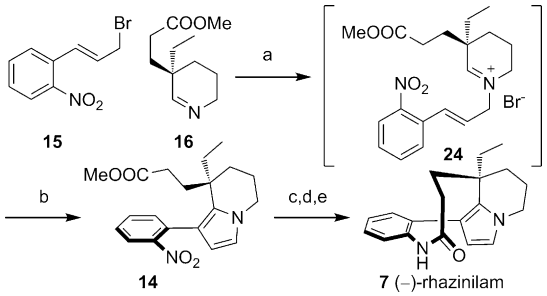
Scheme 1. Retrosynthetic analysis of (−)-rhazinilam (**7**) and (−)-leucomidine B (**8**).



Scheme 2. Synthesis of the tetrahydropyridine **16**. a) Ethanedithiol, $Hf(OTf)_4$, (0.05 equiv), CH_2Cl_2, 95%; b) $LiBH_4$, THF; c) $TMSCHN_2$, MeOH, 95% for two steps; d) MsCl, NEt_3, CH_2Cl_2; e) NaN_3 (2.0 equiv), DMF, 50°C, 83% for two steps; f) IBX, TBAB, AcOH/DMSO/H_2O (1:8:1); g) PPh_3, THF/H_2O (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.

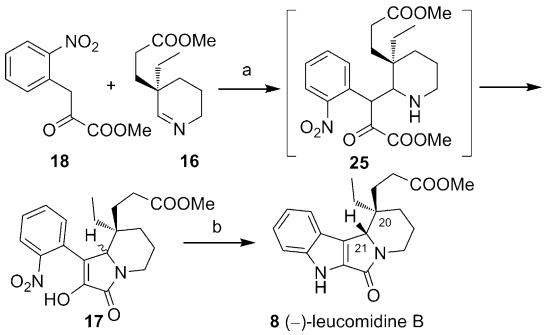
was converted into the 1,3-dithiolane **19** in 95% yield.[23] Chemoselective reduction of the ester to the alcohol ($LiBH_4$) and susbsequent esterification of the carboxylic acid afforded **20**. The primary alcohol was subsequently transformed into the azide **22** via the mesylate intermediate **21**. Deprotection of the dithiolane was realized using a modified literature procedure (IBX, TBAB, AcOH, DMSO/H_2O) 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 BH_3 instead of $LiBH_4$ 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 imminium salt **24**, which upon heating in toluene in the presence of freshly prepared Ag_2CO_3 (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) Ag_2CO_3, toluene, 110°C, 1 h, 60% for two steps; c) Pd/C, H_2, MeOH; d) KOH, MeOH/H_2O (1:1) e) EDC, DMAP, NEt_3, CH_2Cl_2, 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, H_2, 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 $C(sp^2)$–$C(sp^2)$ 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: $[\alpha]_D$ −18.6 (*c* 0.3, $CHCl_3$); natural: $[\alpha]_D$ −18 (*c* 0.3, $CHCl_3$)}. We have also synthesized (+)-leucomidine B (*ent*-**8**) from *ent*-**16** by using exactly the same synthetic scheme {$[\alpha]_D$ +14.3 (*c* 0.3, $CHCl_3$)}. 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 B (**8**).

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