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Aza variant of intramolecular nucleophile-catalyzed aldol lactonization (NCAL): formal synthesis of (3*S*,4*R*) and (3*R*,4*S*) 4-(hydroxymethyl)pyrrolidin-3-ol

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ABSTRACT

Aza variant of intramolecular catalytic, asymmetric nucleophile-catalyzed, aldol lactonization (NCAL) reaction has been explored to synthesize β-lactone fused nitrogen heterocycles as aza sugars' precursors by employing achiral amino acids. The utility of these bicyclic β-lactones is presented by the formal synthesis of aza sugars, (3*S*,4*R*) and (3*R*,4*S*) 4-(hydroxymethyl)pyrrolidin-3-ol.

1. Introduction

Polyhydroxylated pyrrolidines, piperidines (often called amino or aza sugars), and their synthetic analogs have attracted considerable interest due to their ability to mimic sugars.[1] Their often potent inhibitory activity toward glycosidases and glycosyltransferases of various species makes them useful in a wide range of potential therapeutic areas, such as viral infections,[2] cancer,[3] diabetes,[4] tuberculosis,[5] lysosomal storage diseases,[6] and parasitic protozoa.[7] Hydroxylated-piperidine structural framework is found in a wide variety of bio-actives, such as *cis*-3-hydroxypipecolic acid as a constituent of antibiotic tetrazomine,[8] isofebrifugine,[9] and 1-deoxygalactonojirimycin.[6,10] On the other hand, *cis*-3-hydroxyproline structural motif is a part of cyclothialidine[11] (a potent DNA-gyrase inhibitor), slaframine,[12] castanospermine,[13] and detoxinine.[14] For the synthesis of *cis*-3-hydroxy-2-hydroxymethylpyrrolidines (the 'azaDNA' analog) there are only a few syntheses reported in the literature.[15] In recent years, 4-hydroxymethyl-pyrrolidin-3-ol, a precursor for BCX-4208 and its analogs, has been the target of several synthetic approaches of which many are multi-steps or selectivity deficient (Fig. 1).[16] It is therefore necessary to develop new short routes to this class of compounds.

Derivatives of cinchona alkaloids have shown great promise as catalyst for a broad range of asymmetric transformations thereby providing access to chiral products of high enantiopurity.[17] Recently, Romo et al. have reported a high enantioselective synthesis of a series of bicyclic β-lactone fused carbocycles,[18] pyrrolidinone[19a] or tetrahydrofurans[19b] via intramolecular nucleophile-catalyzed aldol lactonization (NCAL) of aldehyde/keto acids (Fig. 2). Inspired

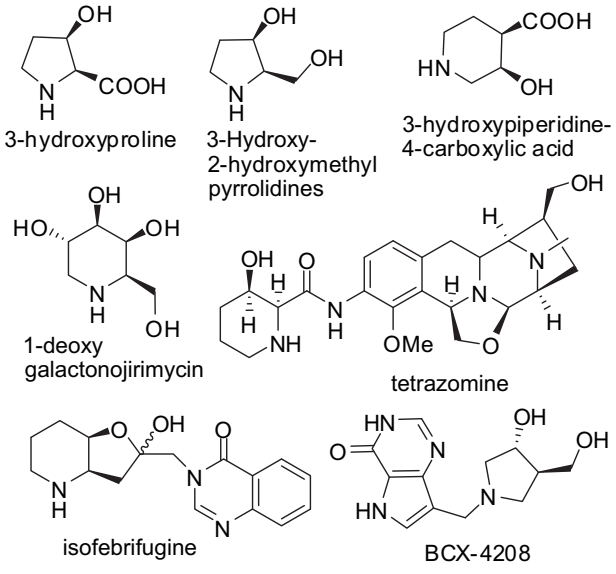

Fig. 1. Structures of aza sugars and related molecules.

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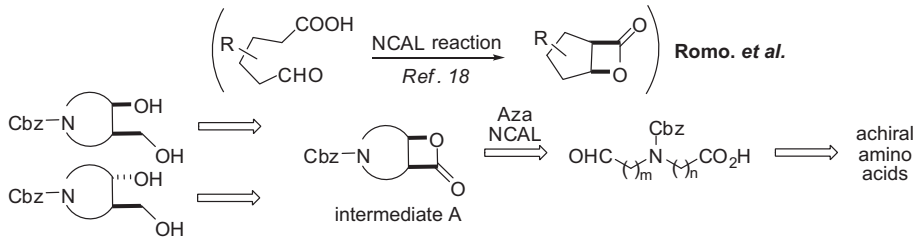
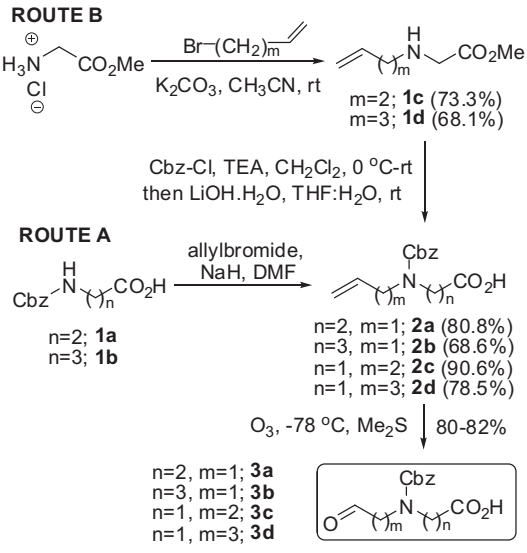


Fig. 2. Retrosynthetic analysis.

by this work, we thought it worthwhile to develop the general synthetic strategy toward the chiral synthesis of several *cis*-aza sugars and related molecules as depicted in Fig. 2.

2. Results and discussion

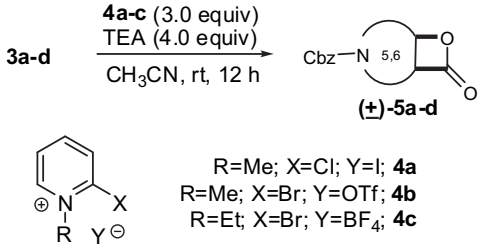
Achiral amino acids (**3a**–**d**) required as the starting point for NCAL reactions were prepared either by N-allylation of Cbz-AlaOH (**1a**[20]→**2a**) or Cbz-GABA (**1b**[20]→**2b**) followed by ozonolysis (route A) to afford **3a**,**b** or by a three-step procedure comprising (i) N-ω-alkenylation of glycine methyl ester[21] (**1c**,**d**), (ii) one pot Cbz protection, hydrolysis of ester group (**2c**,**d**), and (iii) subsequent ozonolysis (route B), to give aldehyde-acids **3c**,**d** (Scheme 1). The



Scheme 1. Synthesis of aldehyde-acids **3a**–**d**.

scope of intramolecular aza-NCAL reaction was studied using substrates **3a**–**d** and Mukaiyama's reagent **4a** under conditions as described by Romo et al.[18a] The reactions were performed by slow syringe pump addition of aldehyde-acids **3a**–**d** over a period of 10 h to a magnetically stirred solution of pyridinium salt **4a** and TEA in acetonitrile at room temperature (method A). The results are summarised in Table 1. It was found that the reactions with **3a** and **3b** afforded racemic β-lactones, **5a** and **5b** in 53% and 51% yield, respectively (Table 1, entries 1 and 2). However, the reaction with aldehyde-acid **3c** gave only the decomposed product (Table 1, entry 3).[22] Use of *N*-methyl-2-bromopyridinium triflate (**4b**)[18b] (method B) and *N*-ethyl-2-bromopyridinium tetrafluoroborate (**4c**) (method C) greatly improved efficiency of the reaction and better yields of the cyclised products were obtained (Table 1, entries 1–4). These results were in conformity with the observations of Romo et al.[18b]

Table 1
Optimization of the racemic aza-NCAL reactions

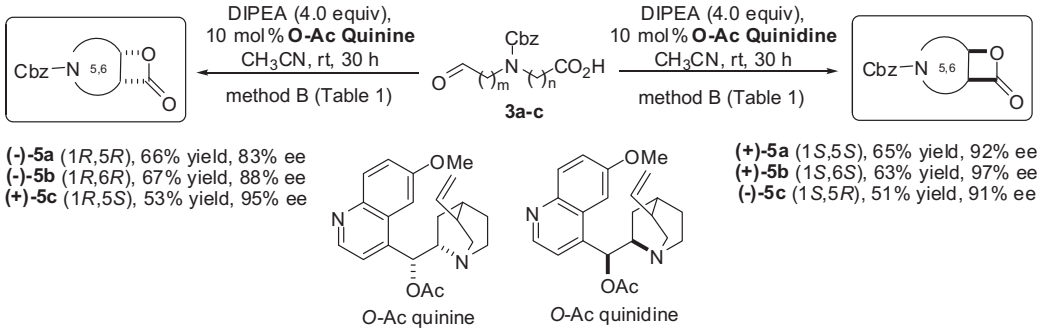


Entry	Aldehyde-acid	(±)-Bicyclic β-lactone	Method[a]	Yield[b] (%)
1	**3a**	**5a**	A	53
			B	76
			C	69
2	**3b**	**5b**	A	51
			B	71
			C	63
3	**3c**	**5c**	A	—[c]
			B	55
			C	51
4	**3d**	**5d**	B	53
			C	52

[a] Substrates **3a**–**d** were added by syringe pump. Method A: **4a** (3.0 equiv), addition time (10 h). Method B: **4b** (3.0 equiv), addition time (3 h). Method C: **4c** (3.0 equiv), addition time (3 h).
[b] Isolated yields.
[c] *N*-Benzyloxycarbonyl-4,5-dihydro-1*H*-pyrrole-2-carboxylic acid was isolated albeit in low yields.

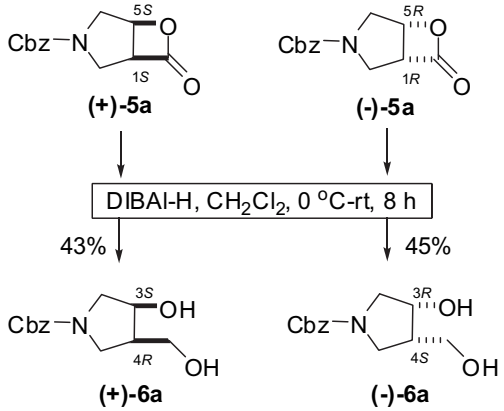
Having optimized the reaction conditions, asymmetric NCAL reactions of substrates **3a**–**c** using chiral amine catalysts were studied next (Scheme 2). It was observed that slow addition of aldehyde-acids **3a**–**c** to a solution of *O*-acetylquinidine,[23] Mukaiyama's reagent **4b**, and DIPEA in CH_3CN gave the enantiomeric bicyclic lactones, (+)-**5a** (65%), (+)-**5b** (63%), and (−)-**5c** (51%) with an ee of 92, 97, and 91%, respectively, as determined by chiral HPLC. Likewise the enantiomeric bicyclic lactones (−)-**5a** (66%), (−)-**5b** (67%), and (+)-**5c** (53%) were synthesized, using *O*-acetylquinine[24] with an ee of 83, 88, and 95%, respectively (Scheme 2).

The (1*S*,5*S*) configuration of bicyclic lactone (+)-**5a** was confirmed by its reduction with DIBAl-H to the known Cbz protected (3*S*,4*R*) 4-(hydroxymethyl)pyrrolidin-3-ol [(+)-**6a**] in 43% yield,



Scheme 2. Catalytic, asymmetric aza-NCAL reactions.

which was compared with the authentic sample ($[\alpha]_D^{29}$ +2.01 (*c* 0.71, MeOH)) [lit.[25] $[\alpha]_D^{25}$ +2.6 (*c* 0.835, MeOH)]. Likewise, diol (−)-**6a** could also be obtained from lactone (−)-**5a** with an overall yield of 45%, which has not been reported in literature so far ($[\alpha]_D^{29}$ −5.00 (*c* 0.69, MeOH)) (Scheme 3).



Scheme 3. Synthesis of diols (+)-**6a** and (−)-**6a**.

3. Conclusion

In conclusion, we have delineated a formal NCAL strategy for the chiral synthesis of β-lactone fused nitrogen heterocycles where the reactive β-lactone provides a handle for further manipulations. We are currently investigating the scope of this methodology for the synthesis of natural products.

4. Experimental section

4.1. General

All NCAL reactions were done using flame-dried glassware under nitrogen atmosphere. Acetonitrile (CH_3CN), triethylamine (TEA), *N*,*N*-diisopropylethylamine (DIPEA), and dichloromethane (CH_2Cl_2) were distilled over calcium hydride. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck pre-coated (Merch 60 F_{254}) silica gel plates and using ninhydrine or $KMnO_4$ as visualizing agent. Purification was performed by flash chromatography using silica gel (230–400 mesh). NMR spectra were recorded on a Bruker Advance-300 spectrometer. Chemical shifts are reported as parts per million (δ) relative to TMS as internal standard. Mass spectra were recorded on LCQ Advantage MAX (ESI) and JOEL JMS-600H (EI/HRMS) mass spectrometers. IR spectra were recorded on a Perkin–Elmer FT-IR RXI spectrometer. Microanalytical data were obtained using Vario-EL-III elemental analyzer. Optical rotations were determined on an Autopol III polarimeter. Chiral HPLC analyses were performed using Daicel Chiralpak IA column.

4.2. General procedure for N-allylation (2a,b)

*4.2.1. N-Allyl-N-benzyloxycarbonyl-β-alanine (**2a**).* To a cooled (0 °C) suspended stirred solution of NaH (4.48 g, 112.1 mmol, 60% NaH in mineral oil) in anhydrous DMF (25 ml) was added a solution of **1a**[20] (5.0 g, 22.4 mmol) in DMF (25 ml) dropwise under nitrogen. Once the hydrogen evolution ceased, allyl bromide (2.9 ml, 33.6 mmol) was added dropwise into the above heterogeneous solution and stirring was continued for additional 2 h at 0 °C. The reaction mixture was quenched at same temperature by the addition of 1 N HCl to become acidic (pH 2), diluted with water (250 ml), and extracted with ethyl acetate (3×80 ml). The combined organic extracts were washed with brine (2×40 ml), dried (Na_2SO_4), and concentrated in vacuo. The resulting crude oil was purified by flash chromatography over silica gel using ethyl acetate/hexane (3:7) to afford **2a** as clear oil (4.76 g, 80.81%) [found: C, 63.58; H, 6.39; N, 5.12. $C_{13}H_{15}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%]; R_f (1:1, EtOAc/hexane) 0.25; ν_{max} (neat) 3069, 2928, 1688, 1474, 1419, 1249, 1135, 1104, 1032, 990, 926 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33 (5H, br s), 5.75–5.77 (1H, br), 5.13 (4H, br s), 3.93 (2H, br), 3.51–3.56 (2H, t, *J* 6.9 Hz), 2.59 (2H, br); δ_C (75 MHz, $CDCl_3$) 176.7, 156.1, 136.6, 133.5, 128.6, 128.1, 127.9, 117.0, 67.4, 50.5, 43.4, 36.8; MS (ESI) *m*/*z*: 264 $[M+H]^+$.

*4.2.2. N-Allyl-N-benzyloxycarbonyl-GABA (**2b**).* The acid was prepared from **1b**[20] (6.0 g, 25.2 mmol), NaH (5.05 g, 126.4 mmol, 60% NaH in mineral oil), and allyl bromide (3.28 ml, 37.9 mmol) at room temperature in 10 h. Purification by flash chromatography over silica gel using ethyl acetate/hexane (1:4) afforded **2b** as clear oil (4.8 g, 68.57%) [found: C, 64.73; H, 6.96; N, 5.00. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%]; R_f (3:2, EtOAc/hexane) 0.3; ν_{max} (neat) 3020, 2360, 1692, 1597, 1472, 1422, 1216, 1045 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.34 (5H, br m), 5.76 (1H, br), 5.13 (4H, br s), 3.87 (2H, br), 3.31 (2H, br), 2.34 (2H, br), 1.86 (2H, br); δ_C (75 MHz, $CDCl_3$) 178.2, 156.4, 136.7, 133.6, 128.5, 128.1, 127.9, 117.0, 67.4, 49.7, 46.3, 31.2, 23.3; MS (ESI) *m*/*z*: 278 $[M+H]^+$.

4.3. General procedure for mono N-alkenylation (1c,d)

*4.3.1. Methyl N-(but-3-enyl)glycinate (**1c**).* K_2CO_3 (9.39 g, 67.9 mmol) was added to a solution of methyl glycinate·HCl[21] (3.15 g, 35.4 mmol) in CH_3CN (150 ml) and the mixture was stirred for 1 h. 4-Bromo-1-butene (3.0 ml, 29.5 mmol) was added to the mixture and the reaction mixture was stirred for 48 h. The insoluble materials

were filtered off and the filtrate was concentrated under reduced pressure. To the residue was added water (150 ml) and extracted with ethyl acetate (3×60 ml). The combined organic extracts were washed with brine (2×25 ml), dried (Na_2SO_4), and concentrated in vacuo to afford a clear liquid. Purification by flash chromatography on silica gel using ethyl acetate/hexane (4:6→10:0) furnished **1c** as clear oil (3.1 g, 73.28%) [found: C, 58.82; H, 9.10; N, 9.81. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15; N, 9.78%]; R_f (EtOAc) 0.3; ν_{max} (neat) 3020, 1743, 1634, 1437, 1215 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.74–5.88 (1H, m), 5.05–5.15 (2H, m), 3.74 (3H, s), 3.44 (3H, s), 2.67–2.72 (2H, t, *J* 6.9 Hz,), 2.24–2.31 (2H, q, *J* 6.9, 13.8 Hz); δ_C (75 MHz, $CDCl_3$) 172.9, 136.1, 166.6, 51.8, 50.7, 48.5, 34.3; MS (ESI) *m*/*z*: 144 $[M+H]^+$.

*4.3.2. Methyl N-(pent-3-enyl)glycinate (**1d**).* Compound **1d** was prepared from methyl glycinate·HCl (3.15 g, 35.4 mmol), K_2CO_3 (9.39 g, 67.9 mmol), and 5-bromo-1-pentene (3.5 ml, 29.5 mmol). Purification by flash column chromatography on silica gel using chloroform as eluant isolated **1d** as clear oil (3.16 g, 68.10%) [found: C, 61.01; H, 9.28; N, 8.93. $C_8H_{15}NO_2$ requires C, 61.12; H, 9.62; N, 8.91%]; R_f ($CHCl_3$) 0.3; ν_{max} (neat) 3020, 2933, 1740, 1639, 1439, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.76–5.89 (1H, m), 4.96–5.07 (2H, m), 3.74 (3H, s), 3.42 (3H, s), 2.60–2.65 (2H, t, *J* 7.1 Hz), 2.08–2.15 (2H, q, *J* 7.1, 14.4 Hz), 1.56–1.66 (2H, m); δ_C (75 MHz, $CDCl_3$) 173.1, 138.4, 114.8, 51.8, 50.8, 49.1, 31.4, 29.2; MS (ESI) *m*/*z*: 158 $[M+H]^+$.

4.4. General procedure for Cbz introduction and hydrolysis (2c,d)

*4.4.1. N-(Benzyloxycarbonyl)-N-(but-3-enyl)-glycine (**2c**).* To a cooled (0 °C) stirred solution of **1c** (2.63 g, 18.3 mmol) and TEA (5.63 ml, 40.4 mmol) in anhydrous CH_2Cl_2 (45 ml) was added Cbz-Cl (2.97 ml, 21.2 mmol) dropwise under nitrogen. The clear yellow solution was warmed to room temperature and stirred for 2 h, at which point the volatiles were removed under reduced pressure to afford yellow oil. The crude oil was then dissolved in THF/H_2O (4:1, 50 ml) with stirring followed by the addition of $LiOH·H_2O$ (2.31 g, 55.1 mmol) at room temperature. After stirring for 2 h, the reaction mixture was diluted with water (30 ml) and extracted with ether (2×35 ml). The pH of aqueous layer was adjusted to 2–3 by the addition of dilute hydrochloric acid (1:1) at 0 °C and extracted the liberated oil with ethyl acetate (4×50 ml). The combined organic extracts were washed with brine (2×45 ml) and dried (Na_2SO_4). Removal of the solvent in vacuo gave the analytically pure product **2c** as clear oil (4.38 g, 90.68%) [found: C, 63.76; H, 6.40; N, 5.12. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%]; R_f (7:3, EtOAc/hexane) 0.35; ν_{max} (neat) 3020, 2361, 1696, 1475, 1431, 1367, 1217, 1149 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27–7.37 (5H, br m), 5.72–5.78 (1H, m), 5.15–5.19 (2H, d, *J* 11.4 Hz), 5.03–5.07 (2H, app t, *J* 6.9 Hz), 4.04–4.07 (2H, d, *J* 10.5 Hz), 3.43 (2H, br), 2.32 (2H, br); δ_C (75 MHz, $CDCl_3$) 174.5/174.3 (rotamers), 156.8/156.0 (rotamers), 136.4/136.3 (rotamers), 135.0/134.8 (rotamers), 128.57/128.51 (rotamers), 128.1/128.0 (rotamers), 127.8/127.7 (rotamers), 117.2/117.0 (rotamers), 67.7/67.5 (rotamers), 49.4/48.9 (rotamers), 48.4/48.0 (rotamers), 32.9/32.4 (rotamers); MS (ESI) *m*/*z*: 264 $[M+H]^+$.

*4.4.2. N-(Benzyloxycarbonyl)-N-(pent-3-enyl)-glycine (**2d**).* Clear oil (78.49%) [found: C, 64.73; H, 6.77; N, 4.99. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%]; R_f(1:9, MeOH/$CHCl_3$) 0.3; ν_{max} (neat) 2935, 2363, 1699, 1470, 1433, 1221 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28–7.37 (5H, m), 5.71–5.83 (1H, m), 5.15–5.19 (2H, d, *J* 11.9 Hz), 4.96–5.07 (2H, m), 4.02–4.07 (2H, d, *J* 12.6 Hz), 3.33–3.40 (2H, q, *J* 7.1 Hz), 2.01–2.12 (2H, m), 1.61–1.68 (2H, m); δ_C (75 MHz, $CDCl_3$) 175.2/174.8 (rotamers), 156.9/156.0 (rotamers), 137.8/137.6 (rotamers), 136.4, 128.6, 128.2/128.1 (rotamers), 127.9/127.8 (rotamers), 115.3/115.2 (rotamers), 67.8/67.6 (rotamers), 49.1/48.7 (rotamers), 48.5/48.0 (rotamers), 30.9/30.8 (rotamers), 27.5/27.1 (rotamers); MS (ESI) *m*/*z*: 278 $[M+H]^+$.

4.5. General procedure for ozonolysis (3a–d)

Ozone was bubbled through a cooled (−78 °C) solution of **2a** (3.2 g, 11.0 mmol) in 75 ml of anhydrous CH_2Cl_2 for 1 h. After that, a stream of argon was passed through the cooled solution for 30 min to eliminate the excess of ozone. The cooled reaction mixture was then quenched with excess of Me_2S (3.57 ml, 48.6 mmol), allowed to warm up to room temperature and treated with cold water (40 ml), extracted with CH_2Cl_2 (3×45 ml), dried (Na_2SO_4), and concentrated in vacuo to obtain the aldehyde **3a** (2.59 g, 80.4%). Similarly **3b–d** were obtained from **2b–d** in 81–82% and were used immediately for NCAL reaction without any further purification.

4.6. *N*-Methyl-2-bromopyridinium triflate (4b)[18b]

Pyridinium salt **4b** was prepared from 2-bromopyridine (2.0 ml, 20.9 mmol) and methyl trifluoromethanesulfonate (2.3 ml, 20.9 mmol) in CH_2Cl_2 (10 ml) according to the literature method as white crystalline solid (6.46 g, 95.98%); mp 158–160 °C; ν_{max} (KBr) 3087, 1616, 1491, 1443, 1267, 1156, 1032 cm^{-1}; δ_H (300 MHz, $CDCl_3$+CD_3OD) 9.10–9.12 (1H, d, *J* 5.2 Hz), 8.34–8.40 (1H, m), 8.27–8.30 (1H, d, *J* 7.2 Hz), 8.0–8.05 (1H, m), 4.48 (3H, s); δ_C (75 MHz, $CDCl_3$) 149.0, 146.3, 133.9, 127.1, 122.5, 118.2, 50.8.

4.7. General procedure for the racemic aza-NCAL reaction as described for (±)-5a

*4.7.1. Benzyl 7-oxo-6-oxa-3-azabicyclo[3.2.0]heptane-3-carboxylate [(±)-**5a**]. Method B*: To a stirred solution of Mukaiyama's reagent **4b** (1.65 g, 5.13 mmol, 3.0 equiv) and TEA (0.95 ml, 6.85 mmol, 4.0 equiv) in CH_3CN (30 ml) at 25 °C was added via syringe pump a solution of aldehyde-acid **3a** (0.45 g, 1.71 mmol) in CH_3CN (20 ml) over a period of 3 h. Stirring of the resulting dark red solution was continued for another 12 h. The volatiles were removed under reduced pressure and to the crude reaction mixture were added ethyl acetate (150 ml) and saturated aqueous NH_4Cl (150 ml). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2×50 ml). The combined organic phases were washed with brine (100 ml), dried (Na_2SO_4), filtered, and concentrated to afford a brown residue. Purification of the crude residue by flash chromatography on SiO_2 using ethyl acetate/hexane (13:7) afforded the β-lactone-**5a** as light yellow oil (0.7 g, 76.07%) [found: C, 63.23; H, 5.41; N, 5.65. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.67%]; R_f (7:3, EtOAc/hexane) 0.35; ν_{max} (neat) 1836, 1705, 1423, 1356, 1261, 1227, 1187, 1114 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.40 (5H, m, Ar*H*), 5.15 (2H, br s, PhCH_2), 5.09–5.12 (1H, dd, *J* 4.0, 5.9 Hz, *H*-5), 4.23–4.28 (2H, br m, *H*-2+*H*-4), 4.08–4.12 (1H, m, *H*-1), 3.29–3.35 (2H, m, *H*-2′+*H*-4′); δ_C (75 MHz, $CDCl_3$) 168.6 (C=O, lactone), 155.0 (C=O, carbamate), 136.1 (qC), 128.5, 128.2, 128.0 (ArC), 74.9/74.3 (C-5, rotamers), 67.5 (PhCH_2), 56.1/55.4 (C-1, rotamers), 49.6 (C-4), 45.6 (C-2); HRMS (ESI): $[M+H]^+$ found 248.0919. $C_{13}H_{14}NO_4$ requires 248.0922.

*4.7.2. Benzyl 7-oxo-8-oxa-3-azabicyclo[4.2.0]octane-3-carboxylate [(±)-**5b**].* This lactone was prepared from oxo-acid **3b** (0.286 g, 1.02 mmol), pyridinium salt **4b** (0.989 g, 3.07 mmol), and TEA (0.49 ml, 3.55 mmol). Purified by flash column chromatography using ethyl acetate/CH_2Cl_2 (7:93) as eluant isolated **5b** as clear viscous oil (0.19 g, 71.16%) [found: C, 64.24; H, 5.81; N, 5.34. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36%]; R_f (1:9, EtOAc/CH_2Cl_2) 0.5; ν_{max} (neat) 1826, 1698, 1421, 1353, 1290, 1224, 1117,

1052 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (5H, br s, Ar*H*), 5.08–5.21 (2H, m, PhC*H*$_2$), 4.74–4.80 (1H, br d, *J* 15.6 Hz, *H*-1), 4.42–4.47 (0.5H, d, *J* 15.6 Hz, *H*-2, rotamers), 4.32–4.37 (0.5H, d, *J* 15.6 Hz, *H*-2, rotamers), 3.82–3.87 (1H, m, *H*-6), 3.67–3.69 (1H, br, *H*-4), 3.46–3.56 (1H, td, *J* 4.5, 12.6 Hz, *H*-4′), 3.36–3.41 (1H, d, *J* 15.6 Hz, *H*-2′), 2.09–2.18 (1H, app t, *J* 15.5 Hz, *H*-5), 1.89–2.02 (1H, m, *H*-5′); δ_C (75 MHz, $CDCl_3$) 169.6 (C=O, lactone), 155.8 (C=O, carbamate), 136.4 (qC), 128.6, 128.2, 127.9 (ArC), 69.1/68.7 (C-1, rotamers), 67.5 (PhCH_2), 47.6 (C-6), 42.0/41.5 (C-2, rotamers), 39.9 (C-4), 19.7 (C-5); HRMS (ESI): $[M+H]^+$ found 262.1080. $C_{14}H_{16}NO_4$ requires 262.1079.

*4.7.3. Benzyl 7-oxo-8-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate [(±)-**5c**].* This lactone was prepared from oxo-acid **3c** (0.225 g, 0.84 mmol), pyridinium salt **4b** (0.819 g, 2.54 mmol), and TEA (0.47 ml, 3.39 mmol). Purified by flash column chromatography using ethyl acetate/CH_2Cl_2 (1:49) as eluant isolated **5c** as viscous oil (0.115 g, 55.02%) [found: C, 63.05; H, 5.39; N, 5.61. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.67%]; R_f (1:9, EtOAc/CH_2Cl_2) 0.6; ν_{max} (neat) 1837, 1708, 1422, 1347, 1306, 1266, 1216, 1108, 1059 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.36 (5H, m, Ar*H*), 5.53–5.65 (1H, br, *H*-1), 5.15–5.17 (3H, m, PhCH_2+*H*-5), 4.12–4.19 (1H, app t, *J* 9.7 Hz, *H*-3), 3.37–3.46 (1H, td, *J* 6.2, 11.5 Hz, *H*-3′), 2.29–2.36 (1H, dd, *J* 6.2, 14.8 Hz, *H*-4), 1.87–2.00 (1H, m, *H*-4′); δ_C (75 MHz, $CDCl_3$) 166.7 (C=O, lactone), 153.3 (C=O, carbamate), 135.9 (qC), 128.7, 128.4, 128.2 (ArC), 77.8 (C-5), 70.2/69.8 (C-1, rotamers), 67.9 (PhCH_2), 44.0 (C-3), 29.1 (C-4); HRMS (ESI): $[M+Na]^+$ found 270.0741. $C_{13}H_{13}NNaO_4$ requires 270.0737.

*4.7.4. Benzyl 8-oxo-7-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate [(±)-**5d**].* This lactone was prepared from oxo-acid **3d** (0.41 g, 1.46 mmol), pyridinium salt **4b** (1.418 g, 4.4 mmol), and TEA (0.81 ml, 5.87 mmol). Purified by flash column chromatography using ethyl acetate/hexane (3:7) as eluant isolated **5d** as viscous oil (0.202 g, 52.74%) [found: C, 64.29; H, 5.65; N, 5.39. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36]; R_f (1:1, EtOAc/hexane) 0.45; ν_{max} (neat) 1832, 1703, 1418, 1310, 1216, 1114, 1037 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35 (5H, br s, Ar*H*), 5.80–5.82 (0.5H, d, *J* 6.6 Hz, *H*-1, rotamers), 5.58–5.60 (0.5H, d, *J* 6.6 Hz, *H*-1, rotamers), 5.12–5.22 (2H, m, PhCH_2), 4.97 (1H, br s, *H*-6), 3.68–3.72 (1H, dd, *J* 3.6, 11.8 Hz, *H*-3), 3.36–3.41 (1H, m, *H*-3′), 2.26–2.30 (1H, d, *J* 12.6 Hz, *H*-4), 1.80–1.99 (3H, m, *H*-5+*H*-5′+*H*-4′); δ_C (75 MHz, $CDCl_3$) 170.5/169.9 (C=O, lactone, rotamers), 155.7/154.6 (C=O, carbamate, rotamers), 136.0 (qC), 128.6, 128.4, 128.1 (ArC), 72.1/71.9 (C-6, rotamers), 68.1/68.0 (PhCH_2, rotamers), 59.7/59.5 (C-1, rotamers), 43.0/42.9 (C-3, rotamers), 25.9 (C-4), 16.1/15.8 (C-5, rotamers); HRMS (ESI): $[M+H]^+$ found 262.1094. $C_{14}H_{16}NO_4$ requires 262.1079.

4.8. General procedure for asymmetric aza-NCAL reaction as described for β-lactone-(+)-5a

*4.8.1. (1S,5S)-Benzyl 7-oxo-6-oxa-3-azabicyclo[3.2.0]heptane-3-carboxylate [(+)-**5a**].* To a stirred solution of *O*-acetylquinidine[23] (71 mg, 0.196 mmol), Mukaiyama's reagent **4b** (1.895 g, 5.88 mmol), and DIPEA (1.36 ml, 7.84 mmol) in CH_3CN (35 ml) was added a solution of aldehyde-acid **3a** (0.52 g, 1.96 mmol) in CH_3CN (30 ml) via syringe pump over a period of 3 h. After the addition was completed, the reaction was stirred for additional 30 h at 25 °C. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate (150 ml) and saturated NH_4Cl (100 ml). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2×50 ml). The combined organic phases were washed with brine (100 ml), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash chromatography on SiO_2 using ethyl acetate/hexane (13:7) afforded the β-lactone-(+)-**5a** as light yellow oil (0.315 g, 64.94%). $[\alpha]_D^{29}$ +111.4 (*c* 0.20, $CHCl_3$). Enantiomeric excess (ee) was determined to be 92% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=99:1, flow rate 0.6 ml/min, λ_{max} 213.9 nm), $t_{1S,5S}$=20.74 min (major), $t_{1R,5R}$=22.66 min (minor). All other spectroscopic data matched that displayed by (±)-**5a**.

*4.8.2. (1S,6S)-Benzyl 7-oxo-8-oxa-3-azabicyclo[4.2.0]octane-3-carboxylate [(+)-**5b**].* This lactone was prepared from oxo-acid **3b** (0.25 g, 0.89 mmol), pyridinium salt **4b** (0.864 g, 2.68 mmol), DIPEA (0.62 ml, 3.58 mmol), and *O*-acetylquinidine (32 mg, 0.089 mmol). Purification by flash column chromatography on silica gel using ethyl acetate/CH_2Cl_2 (7:93) as eluant gave (+)-**5b** as viscous oil (0.147 g, 63.09%). $[\alpha]_D^{29}$ +118.7 (*c* 1.09, MeOH). Enantiomeric excess (ee) was determined to be 97% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=99:1, flow rate 0.6 ml/min, λ_{max} 209 nm), $t_{1S,6S}$=20.98 min (major), $t_{1R,6R}$=32.31 min (minor). All other spectroscopic data matched that displayed by (±)-**5b**.

*4.8.3. (1S,5R)-Benzyl 7-oxo-8-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate [(−)-**5c**].* This lactone was prepared from oxo-acid **3c** (0.29 g, 1.09 mmol), pyridinium salt **4b** (1.05 g, 3.27 mmol), DIPEA (0.76 ml, 4.37 mmol), and *O*-acetylquinidine (40 mg, 0.109 mmol). Purification by flash column chromatography on silica using ethyl acetate/CH_2Cl_2 (1:49) as eluant gave (−)-**5c** as viscous oil (0.137 g, 50.74%). $[\alpha]_D^{27}$ −132.4 (*c* 0.16, MeOH). Enantiomeric excess (ee) was determined to be 91% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=98:2, flow rate 0.8 ml/min, λ_{max} 213 nm), $t_{1R,5S}$=8.82 min (minor), $t_{1S,5R}$=11.64 min (major). All other spectroscopic data matched that of the racemic compound (±)-**5c**.

*4.8.4. (1R,5R)-Benzyl 7-oxo-6-oxa-3-azabicyclo[3.2.0]heptane-3-carboxylate [(−)-**5a**].* The lactone was prepared from aldehyde-acid **3a** (0.348 g, 1.31 mmol), pyridinium salt **4b** (1.268 g, 3.93 mmol), DIPEA (0.91 ml, 5.25 mmol), and *O*-acetylquinine[24] (48 mg, 0.13 mmol) following the procedure as described for (+)-**5a**. Purification by flash chromatography on SiO_2 using ethyl acetate/hexane (13:7) gave the (−)-**5a** as colorless oil (0.214 g, 66.04% yield). $[\alpha]_D^{29}$ −39.1° (*c* 0.44, $CHCl_3$). Enantiomeric excess (ee) was determined to be 83% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=99:1, flow rate 0.6 ml/min, λ_{max} 213.9 nm), $t_{1S,5S}$=20.56 min (minor), $t_{1R,5R}$= 22.42 min (major). All other spectroscopic data matched with (±)-**5a**.

*4.8.5. (1R,6R)-Benzyl 7-oxo-8-oxa-3-azabicyclo[4.2.0]octane-3-carboxylate [(−)-**5b**].* This lactone was prepared from oxo-acid **3b** (0.195 g, 0.698 mmol), pyridinium salt **4b** (0.674 g, 2.09 mmol), DIPEA (0.48 ml, 2.79 mmol), and *O*-acetylquinine (25 mg, 0.069 mmol). Purification by flash column chromatography on silica gel using ethyl acetate/CH_2Cl_2 (7:93) as eluant gave (−)-**5b** as viscous oil (0.12 g, 67.03%). $[\alpha]_D^{29}$ −63.3 (*c* 1.11, MeOH). Enantiomeric excess (ee) was determined to be 88% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=99:1, flow rate 0.6 ml/min, λ_{max} 209 nm), $t_{1S,6S}$=20.05 min (minor), $t_{1R,6R}$=33.36 min (major). All other spectroscopic data matched with the racemic compound (±)-**5b**.

*4.8.6. (1R,5S)-Benzyl 7-oxo-8-oxa-2-azabicyclo[4.2.0]octane-2-carboxylate [(+)-**5c**].* This lactone was prepared from oxo-acid **3c** (0.2 g, 0.753 mmol), pyridinium salt **4b** (0.728 g, 2.26 mmol), DIPEA (0.52 ml, 3.01 mmol), and *O*-acetylquinine (27 mg, 0.075 mmol). Purification by flash column chromatography on silica using ethyl

acetate/CH_2Cl_2 (1:49) as eluant gave (+)-**5c** as viscous oil (0.098 g, 52.68%). $[\alpha]_D^{28}$ +67.7 (*c* 0.37, MeOH). Enantiomeric excess (ee) was determined to be 95% by chiral stationary phase HPLC analysis using Daicel Chiralpak IA column (MtBE/EtOH=98:2, flow rate 0.8 ml/min, λ_{max} 213 nm), $t_{1R,5S}$=8.76 min (major), $t_{1S,5R}$=11.63 min (minor). All other spectroscopic data matched with the racemic compound (±)-**5c**.

4.9. General procedure for reduction as described for diol (+)-6a

*4.9.1. (3S,4R)-N-Benzyloxycarbonyl-4-(hydroxymethyl)pyrrolidin-3-ol [(+)-**6a**].* To a magnetically stirred solution of (+)-**5a** (0.17 g, 0.687 mmol) in CH_2Cl_2 (5.3 ml) was added dropwise a solution of DIBAl-H (1.0 M in toluene, 0.738 ml, 0.742 mmol) at 0 °C. After 5 min, the solution was warmed to room temperature and stirred overnight. The reaction mixture was then cooled to 0 °C, diluted with ethyl acetate (2.4 ml), and quenched with acetone (1.5 ml) and Rochelle's salt (4.0 ml). The mixture was vigorously stirred at 25 °C for 10 h. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×4 ml). The combined organic layers were washed with brine (8 ml), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on SiO_2 using MeOH/ethyl acetate (1:9) gave the diol (+)-**6a** as a colorless oil (74 mg, 43.19% yield) [found: C, 62.23; H, 6.75; N, 5.52. $C_{13}H_{17}NO_4$ requires C, 62.14; H, 6.82; N, 5.57%]; R_f (1:9, MeOH/EtOAc) 0.3; $[\alpha]_D^{29}$ +2.01 (*c* 0.71, MeOH) [lit.[25] $[\alpha]_D^{25}$ +2.6 (*c* 0.835, MeOH)]; ν_{max} (neat) 3389, 2920, 1682, 1433, 1358, 1216, 1136, 1097 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28–7.32 (5H, m, Ar*H*), 5.04–5.14 (2H, m, PhC*H*$_2$), 4.41 (1H, br s, *H*-3), 3.78–3.83 (2H, t, *J* 7.8 Hz, C*H*$_2$OH), 3.44–3.56 (3H, m, *H*-2+*H*-2′+*H*-5), 3.32–3.39 (1H, t, *J* 10.5, *H*-5′), 2.28–2.29 (1H, br, *H*-4); δ_C (75 MHz, $CDCl_3$) 155.5 (C=O), 136.8 (qC), 128.6, 128.1, 127.9 (ArC), 72.3/71.5 (C-3, rotamers), 67.1 (PhCH_2), 60.3 (CH_2OH), 55.2/54.9 (C-2, rotamers), 45.9/45.6 (C-5, rotamers), 45.1/44.3 (C-4, rotamers); MS (ESI) *m*/*z*: 252 $[M+H]^+$; HRMS (ESI): $[M+H]^+$ found 252.1216. $C_{13}H_{18}NO_4$ requires 252.1235.

*4.9.2. (3R,4S)-N-Benzyloxycarbonyl-4-(hydroxymethyl)pyrrolidin-3-ol [(−)-**6a**].* The diol was prepared from lactone (−)-**5a** (0.142 g, 0.574 mmol) and DIBAl-H (1.0 M in toluene, 0.618 ml, 0.62 mmol). Purification by flash chromatography on SiO_2 using MeOH/ethyl acetate (1:9) gave the diol (−)-**6a** as colorless oil (58 mg, 44.16% yield). $[\alpha]_D^{29}$ −5.0 (*c* 0.69, MeOH). All other spectroscopic data matched with diol (+)-**6a**.

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Supplementary data

^1H, ^{13}C, and HSQC spectral data for lactones (±)-**5a**–**d** and diol (+)-**6a**, chiral HPLC data for **5a**–**c**, and ^1H and ^{13}C spectral data for **4b** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.10.085. These data include MOL files and InChIKeys of the most important compounds described in this article.

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