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Diels–Alder approaches to ring-functionalized cyclic β-amino acids

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Abstract

Catalytic asymmetric Diels–Alder reactions with aminodiene **1** and desymmetrized fumarate **8** were used for efficient access to dihydroxylated *cis*- and *trans*-aminocyclohexane β-amino acids.

Keywords: enantioselective Diels–Alder reaction; β-amino acids; aminocyclohexanecarboxylate; scandium triflate; Curtius rearrangement.

The use of oligomers of β-amino acids as novel foldamers that could mimic physical characteristics and biological functions of peptides has led to a considerable need for efficient synthetic routes toward the enantiopure building blocks.[1] In particular, water-soluble hydroxylated or aminated derivatives of cyclohexyl β-amino acids have attractive properties and a high intrinsic propensity for helical folding.[2,3] We now report an efficient approach toward dihydroxylated *cis*- and *trans*-aminocyclohexanecarboxylic acids that takes advantage of modern catalytic asymmetric Diels–Alder reactions (Fig. 1).

Starting with readily available *N*-Cbz-protected aminodiene **1**,[4,5] we explored the use of Kobayashi's chiral scandium catalyst for the Lewis acid-mediated Diels–Alder reaction with acyl-1,3-oxazolidin-2-one **2** (Scheme 1).[6,7] After a reaction time of 24 h, *endo* product **3** was isolated in 92% yield and in 90% ee.[8] The corresponding *exo*-product was also identified in 6% yield in the reaction mixture. After saponification of **3** and benzyl ester formation, dihydroxylation proceeded smoothly to give the desired diol **4** in 74% overall yield from **1**.

We also explored an alternative route to the β-amino acid building block **4** that took advantage of a recently reported nucleophilic catalyst by MacMillan.[9] Addition of 20 mol% of the phenylalanine-derived imidazolidinone **7** to a mixture of aminodiene **1** and acrolein in nitromethane/water provided cyclohexene **6** as a 14:1 mixture of *endo*:*exo* diastereomers

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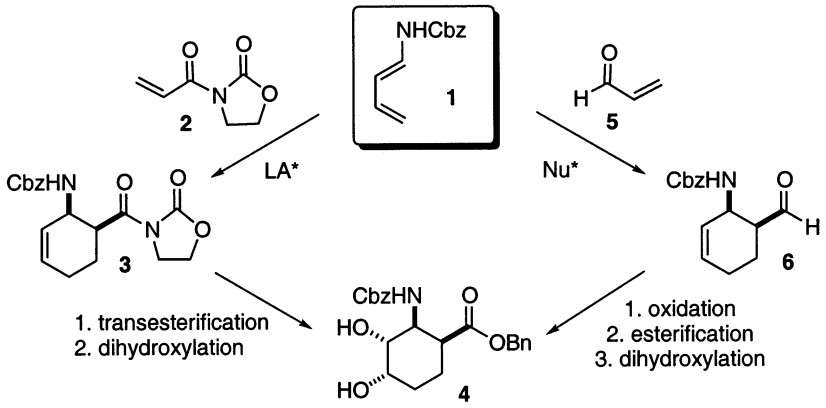
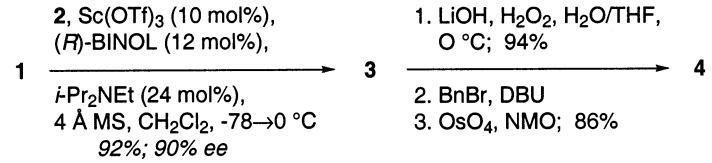
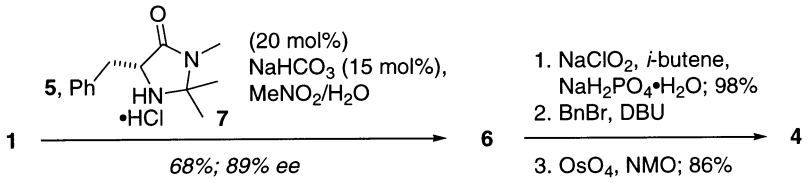


Figure 1. Catalytic asymmetric Diels–Alder approaches toward *cis*-aminocyclohexanecarboxylate **4**



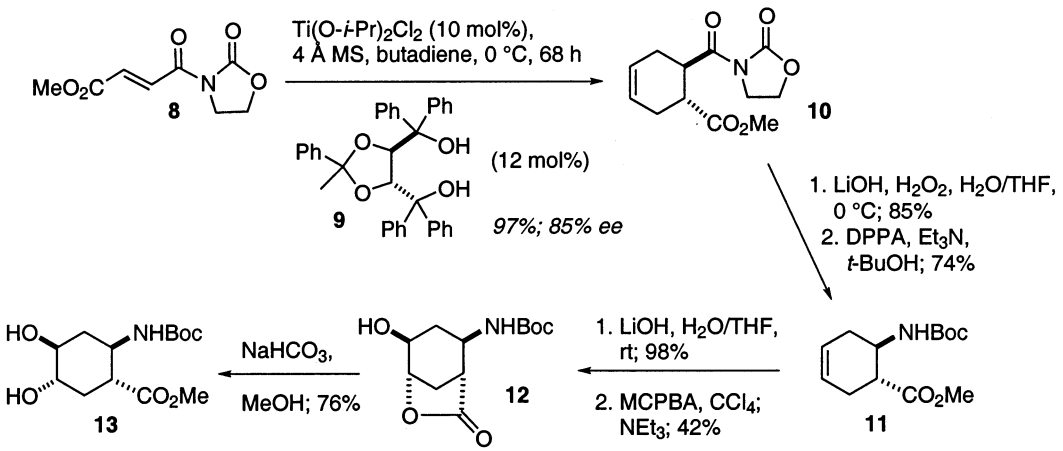
Scheme 1. Chiral Lewis acid Diels–Alder approach

(Scheme 2). The use of 15 mol% of $NaHCO_3$ was essential in this reaction due to the instability of the aminodiene component towards protic acid and the pH-dependence of the reaction rate. Pure **6** was isolated in 68% yield and in 89% ee after column chromatography and readily converted to **4** by oxidation, esterification and dihydroxylation with catalytic OsO_4 under the Upjohn conditions. Both the Lewis acid- and the nucleophile-catalyzed asymmetric Diels–Alder routes, thus provided the desired dihydroxylated β-amino acid **4** in high enantiomeric excess that could be further increased to >98% by crystallization of **3**.[10]



Scheme 2. Nucleophile-catalyzed Diels–Alder approach

While epimerization at the carbonyl α-carbon of *cis*-aminocyclohexanecarboxylates has been used for the preparation of the corresponding *trans*-isomers,[3] we found that this approach was unreliable in providing preparative scale access to the desired *trans*-analogs of **4**. In contrast, a stereoselective strategy using Narasaka's chiral titanium catalyst was much more efficient (Scheme 3).[11] Treatment of fumarate hemi-ester **8**[12] with butadiene and 10 mol% of titanium complex in the presence of 12 mol% of chiral diol **9** led to a slow, but highly enantioselective, Diels–Alder process. If the reaction was allowed to proceed for 68 h at 0°C in the presence of 4 Å molecular sieves, a quantitative yield of **10** in 85% ee was isolated.[13] Increasing the reaction temperature considerably accelerated the process, but was accompanied by significant reductions in enantioselectivity. A single recrystallization of **10** led to material of >98% ee.



Scheme 3. Chiral Lewis acid Diels–Alder/Curtius rearrangement approach

Cyclohexene diester **10** was selectively saponified at 0°C, and the resulting acid was subjected to a Curtius rearrangement with DPPA in *t*-butanol (Scheme 3).[1e,14] While this strategy provided a convenient access to the desired *trans*-aminocyclohexenecarboxylate **11**, introduction of the backbone hydroxyl groups that would provide for suitable water-solubility of this β-amino acid building block was problematic. Hydroxylation under a range of reaction conditions only led to mixtures of diastereomers due to lack of facial- and regioselectivity in the attack onto the alkene moiety of **11**. In contrast, exposure of the acid derived from **11** to metachloroperbenzoic acid and in situ cyclization of the intermediate epoxy carboxylate provided the hydroxy lactone **12** as a single diastereomer.[15] Subsequent mild methanolysis led to the all-*trans* tetrasubstituted cyclohexane derivative **13**.[16]

In conclusion, we have been able to identify three stereocontrolled and efficient Diels–Alder approaches toward dihydroxylated *cis*- and *trans*-aminocyclohexanecarboxylates. Both Lewis acid and nucleophilic catalysis are suitable for the preparation of the *cis*-derivative **4** from aminodiene **1**, and a combination of a titanium-catalyzed asymmetric Diels–Alder reaction with fumarate **8** followed by Curtius rearrangement and neighboring group-assisted alkene functionalization provides the *trans*-analog **13**. We expect that building blocks **4** and **13** will be of considerable use for the design of helical, water-soluble β-peptidic foldamers as well as for the synthesis of new chiral ligands for asymmetric catalysis, and further studies toward these goals will be reported in due course.

Acknowledgements

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10. Experimental protocols for preparation of **4**: **(1*R*,6*S*)-[6-(2-oxo-oxazolidine-3-carbonyl)-cyclohex-2-enyl]-carbamic acid benzyl ester** (**3**). To a mixture of $Sc(OTf)_3$ (443 mg, 0.900 mmol), (*R*)-BINOL (309 mg, 1.08 mmol), and 4 Å MS (1.17 g) was added ^{i}Pr$_2$ NEt (279 mg, 376 μL, 2.16 mmol) in dichloromethane (18 mL) at −78°C. The reaction mixture was stirred for 30 min at −78°C, and then solutions of **2** (1.27 g, 9.00 mmol) and **1** (1.83 g, 9.00 mmol) in dichloromethane (9 mL) were added successively via cannula. The resulting solution was slowly warmed to 0°C, stirred at 0°C for 24 h, quenched with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 30:70) to give **3** as a white crystalline solid (2.85 g, 92%, 90% ee) and *exo*-product as a colorless oil (174 mg, 6%). **3**: mp 131.0–133.0°C; $[\alpha]_D$ +151 (*c* 1.16, CH_2Cl_2); ^{1}H NMR δ 7.36–7.25 (m, 5H), 5.90–5.86 (m, 1H), 5.70–5.65 (m, 1H), 5.07–4.93 (m, 3H), 4.75–4.74 (m, 1H), 4.24 (dd, 2H, J = 7.9, 8.3 Hz), 3.91–3.88 (m, 1H), 3.82–3.79 (m, 1H), 3.52–3.48 (m, 1H), 2.16–2.00 (m, 2H), 1.80–1.72 (m, 2H); ^{13}C NMR δ 173.4, 155.7, 153.8, 136.8, 131.3, 128.5, 128.1, 127.8, 125.6, 66.6, 62.3, 45.6, 43.5, 42.8, 24.4, 19.3. **(1*S*,2*R*)-2-Benzyloxycarbonylamino-cyclohex-3-ene carboxylic acid**. To a solution of **3** (2.83 g, 8.22 mmol) in THF (125 mL) and H_2O (34.5 mL) was added 30% H_2O_2 (2.24 g, 6.72 mL, 65.8 mmol) followed by addition of $LiOH{\cdot}H_2O$ (690 mg, 16.4 mmol) at 0°C. The resulting mixture was stirred at room temperature for 38 h, cooled to 0°C, and treated with a 1.35N solution of Na_2SO_3 in H_2O (54 mL) followed by 0.5N $NaHCO_3$ (82 mL). The THF was evaporated in vacuo. The aqueous residue was diluted with H_2O and extracted with CH_2Cl_2 to remove oxazolidinone. The aqueous phase was acidified to pH 1–2 with 5N HCl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 5:95) to give (1*S*,2*R*)-2-benzyloxycarbonylamino-cyclohex-3-ene carboxylic acid as an off-white solid (2.13 g, 94%). **(1*S*,2*R*)-2-Benzyloxycarbonylamino-cyclohex-3-ene carboxylic acid benzyl ester**. To a solution of this acid (118 mg, 0.428 mmol) in acetonitrile (4.0 mL) was added DBU (130 mg, 0.855 mmol) and benzyl bromide (165 mg, 0.964 mmol). The mixture was stirred at room temperature for 7 h. The solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 15:85) to give (1*S*,2*R*)-2-benzyloxycarbonylamino-cyclohex-3-ene carboxylic acid benzyl ester as a colorless oil (158 mg, quant.). **(1*S*,2*S*,3*R*,4*S*)-2-Benzyloxycarbonylamino-3,4-dihydroxy-cyclohexane carboxylic acid benzyl ester** (**4**). To a solution of this ester (147 mg, 0.401 mmol) in *tert*-butyl alcohol (4.0 mL) was added OsO_4 (2.5 wt.% in ^{t}BuOH; 250 μL) and NMO (141 mg, 1.20 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12.5 h. The solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 60:40) to give **4** as a white solid (137 mg, 86%): mp 123.0–124.0°C; $[\alpha]_D$ −46.7 (*c* 1.24, CH_2Cl_2); ^{1}H NMR δ 7.34 (s, 10H), 5.83 (d, 1H, J = 8.7 Hz), 5.18–5.03 (m, 4H), 4.20–4.13 (m, 1H), 4.00–3.94 (m, 2H), 3.57 (d, 1H, J = 5.1 Hz), 3.34 (s, 1H), 3.10–3.00 (m, 1H), 2.12–2.03 (m, 1H), 1.88–1.75 (m, 2H), 1.47–1.39 (m, 1H); ^{13}C NMR δ 173.7, 157.2, 136.3, 135.6, 128.7, 128.6, 128.4, 128.2, 128.1, 71.4, 68.8, 67.1, 66.6, 51.5, 44.1, 27.2, 21.7; HRMS (EI) m/e calculated for $C_{22}H_{25}O_6N$: 399.1682, found: 399.1679.

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16. Experimental protocols for the preparation of **13**: **(1*R*,6*R*)-6-(2-oxo-oxazolidine-3-carbonyl)-cyclohex-3-ene carboxylic acid methyl ester (10)**. To a mixture of $Ti(O^iPr)_2Cl_2$ (54.7 mg, 0.231 mmol) and **9** (147 mg, 0.277 mmol) was added toluene (9.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h, and then transferred to a suspension of 4 Å MS (500 mg) in toluene (9.5 mL). The mixture was cooled to 0°C. A solution of **8** (460 mg, 2.31 mmol) in toluene (13 mL) was added, followed by hexanes (16 mL) and butadiene (7 mL). The reaction mixture was stirred at 0°C for 28 h, treated with 10 mL of butadiene, stirred at 0°C for another 40 h, quenched with H_2O, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 50:50) to give **10** as a white solid (568 mg, 97, 85% ee): mp 100.0–102.0°C; $[\alpha]_D$ −149 (*c* 1.50, CH_2Cl_2); ^1H NMR δ 5.68–5.67 (m, 2H), 4.44–4.38 (m, 2H), 4.08–3.92 (m, 2H), 3.64 (s, 3H), 3.06–2.96 (m, 1H), 2.55–2.40, 2.20–1.95 (2m, 5H); ^{13}C NMR δ 176.1, 175.5, 153.2, 125.0, 124.9, 62.0, 51.9, 42.7, 41.2, 39.8, 28.2, 28.1. **(1*R*,2*R*)-Cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester.** To a solution of **10** (440 mg, 1.74 mmol) in THF (27.0 mL) and H_2O (7.6 mL) was added at 0°C 30% H_2O_2 (473 mg, 1.42 mL, 13.9 mmol)) followed by $LiOH{\cdot}H_2O$ (91.0 mg, 2.17 mmol). The resulting mixture was stirred at room temperature for 18 h, cooled to 0°C, and treated with a 1.35N solution of Na_2SO_3 in H_2O (12.5 mL) followed by 0.5N $NaHCO_3$ (21.8 mL). The THF was evaporated in vacuo. The aqueous residue was diluted with H_2O and extracted with CH_2Cl_2 to remove oxazolidinone. The aqueous phase was acidified to pH 1–2 with 5N HCl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 5:95) to give (1*R*,2*R*)-cyclohex-4-ene-1,2-dicarboxylic acid monomethyl ester as a colorless oil (272 mg, 85%). **(1*R*,6*R*)-6-*tert*-Butoxycarbonylamino-cyclohex-3-ene carboxylic acid methyl ester (11)**. To a solution of the ester (262 mg, 1.42 mmol) in dry ^{t}BuOH (7.5 mL) was added Et_3N (173 mg, 1.71 mmol) and diphenylphosphonyl azide (471 mg, 1.71 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h, and then heated at reflux for 24 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 8:92) to give **11** as a white crystalline solid (270 mg, 74%): mp 83.6–84.2°C; $[\alpha]_D$ −25.1 (*c* 1.12, CH_2Cl_2); IR (neat) 3385, 3032, 2984, 2952, 2926, 1723, 1683, 1525, 1435, 1369, 1312, 1256, 1192, 1168, 1016, 660 cm^{-1}; ^1H NMR δ 5.60–5.67 (m, 2H), 4.64 (br-s, 1H), 4.01 (br-s, 1H), 3.68 (s, 3H), 2.69–2.64 (m, 1H), 2.54–2.46 (m, 2H), 2.44–2.42 (m, 1H), 1.99–1.91 (m, 1H), 1.42 (s, 9H); ^{13}C NMR δ 174.1, 155.1, 125.1, 124.3, 79.4, 51.9, 47.4, 44.8, 31.2, 28.4, 26.6. **(1*R*,6*R*)-6-*tert*-Butoxycarbonylamino-cyclohex-3-ene carboxylic acid**. A solution of **11** (89.7 mg, 0.351 mmol) in THF/water (10:1, 4.4 mL) was treated with $LiOH{\cdot}H_2O$ (73.7 mg, 1.76 mmol). The resulting mixture was stirred at room temperature for 78 h before THF was removed in vacuo. The residue was diluted with water, acidified to pH 1–2 with 5N HCl, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 6:94) to give (1*R*,6*R*)-6-*tert*-butoxycarbonylamino-cyclohex-3-ene carboxylic acid as a colorless oil (82.7 mg, 98%). **(1*R*,2*R*,4*S*,5*S*)-(4-Hydroxy-7-oxo-6-oxa-bicyclo[3.2.1]oct-2-yl)-carbamic acid *tert*-butyl ester (12)**. A solution of this acid (86.2 mg, 0.357 mmol) in CCl_4 (3.6 mL) was treated with *m*-chloroperoxybenzoic acid (67.8 mg, 0.393 mmol) at 0°C for 4 h. Then, triethylamine (79.5 mg, 0.786 mmol) was added. The reaction mixture was heated at 55°C for 3.5 h. The solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (ethyl acetate/hexanes, 50:50) to give slightly impure **12** as a white solid (38.6 mg, 42%) that was carried on without further purification. **(1*R*,2*R*,4*S*,5*S*)-2-*tert*-Butoxycarbonylamino-4,5-dihydroxy-cyclohexane carboxylic acid methyl ester (13)**. A solution of crude **12** (34.9 mg, 0.136 mmol) in MeOH (1.4 mL) was treated with sodium bicarbonate (11.4 mg, 0.135 mmol). The reaction mixture was stirred at room temperature for 27 h. The solvent was removed in vacuo and the residue was purified by chromatography on SiO_2 (ethyl acetate/hexanes, 80:20) to give **13** as a white solid (29.7 mg, 76%): mp 155.0–155.5°C; $[\alpha]_D$ −13.8 (*c* 1.0, MeOH); ^1H NMR (CD_3OD) δ 6.72 (d, 1H, J=8.7 Hz), 4.86 (s, 1H), 3.63 (s, 3H), 3.37–3.24 (m, 2H), 2.45–2.37 (m, 1H), 2.09–1.96 (m, 2H), 1.59–1.28 (m, 11H); ^{13}C NMR (CD_3OD) δ 173.8, 156.1, 78.7, 72.9, 72.4, 51.1, 49.5, 38.5, 33.6, 27.3; HRMS (EI) *m*/*e* calculated for $C_9H_{15}O_6N$ ($M-C_4H_8$): 233.0899, found: 233.0897.