Preparation of Bicyclo[4.3.0]nonanes by an Organocatalytic Intramolecular Diels–Alder Reaction

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The bicyclo[4.3.0]nonane substructure is an abundant structure found in several natural compounds. A novel enantioselective organocatalytic cycloaddition was used to prepare the bicyclo[4.3.0]nonane skeleton.

Introduction

A novel method for producing bicyclo[4.3.0]nonanes, *trans*-fused hexahydroindenes, (Figure 1) has been developed. These types of substructure can be found in several natural compounds. For example, Sata and Fusetani isolated and identified amaminols A (**1**) and B (**2**),[1] which are cytotoxic against P388 murine leukemia cells with an IC_{50} value of 2.1 μg mL^{-1}. Amaminols A (**1**) and B (**2**) contain an interesting *trans*-fused hexahydroindene substructure (Figure 1), most probably formed from a triene through an intramolecular Diels–Alder reaction in nature.

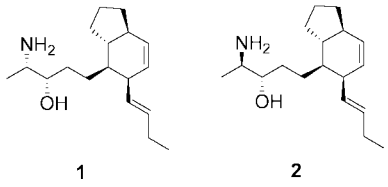

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Figure 1. Structures of amaminols A (**1**) and B (**2**).

Results and Discussion

Natural compounds related to amaminol A (**1**) and B (**2**), such as pulo'upones,[2] indanomycin (X-14547A),[3] 16-deethylindanomycin (A83094A),[4] homoindanomycin,[5] cafamycin,[6] stawamycin,[7] cochleamycin A,[8] ikarugamycin,[9] and lepicidin A[10] have been synthesized by several different methods. The research groups of Roush,[11] Nicolaou,[12] Boeckman,[13] Ley,[14] Kurth,[15] Jones,[16] Paquette,[17] Hase,[18] and Dias[19] have mostly used thermal IMDAs for the preparation of their target molecules. However, the triene precursor for the IMDA has to be chiral itself if a racemic mixture is to be avoided without use of a chiral catalyst. In some syntheses a Lewis acid and a covalently bound chiral auxiliary are used to improve the diastereo- and enantioselectivities of the IMDA cycloaddition. For example, Oppolzer,[20] Takano,[21] and Evans[22] used different covalently bound auxiliaries in their natural product syntheses. Furthermore, Evans has used asymmetric copper catalysts in IMDA during the preparation of isopulo'upone.[23] Burke has used RHDA cycloreversion[24] in the synthesis of these types of compounds. Photocyclization also affords an elegant route to bicyclo[4.3.0]nonanes, which has been demonstrated by Whitesell.[25] However, the preparation of the precursor can be laborious, as in the synthesis of ikarugamycin (15 steps). The oxy-Cope rearrangement approach also provides a short route to bicyclo[4.3.0]-nonanes, as demonstrated by the Paquette group.[26]

During the synthesis of amaminol A (**1**) we became interested in extending our recently developed organocatalytic Diels–Alder reaction to intramolecular cases.[27] The requisite triene starting material for cycloaddition experiments was prepared from readily available methyl sorbate in seven steps by conventional methods.[28] The resulting mixture of triene aldehydes **3** and **4** (Figure 2) was difficult to separate by distillation or chromatography, and was thus used as such, since only **3** would undergo the desired IMDA reaction.

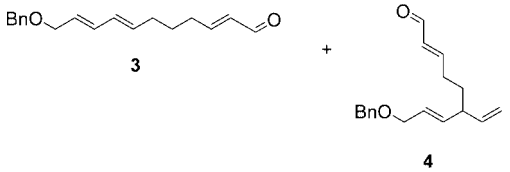

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Figure 2. Starting material mixture used for organocatalytic intramolecular Diels–Alder reactions.

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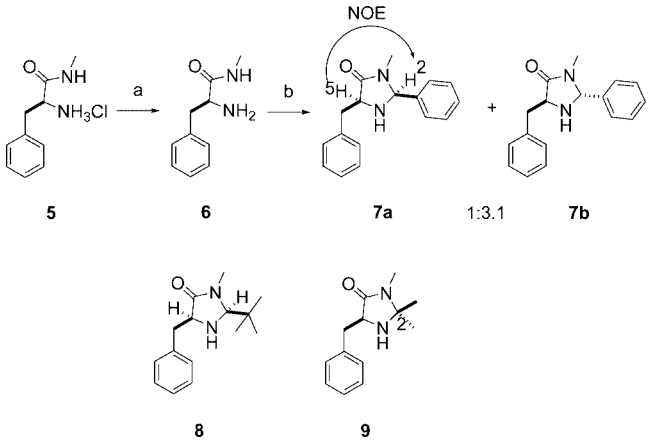
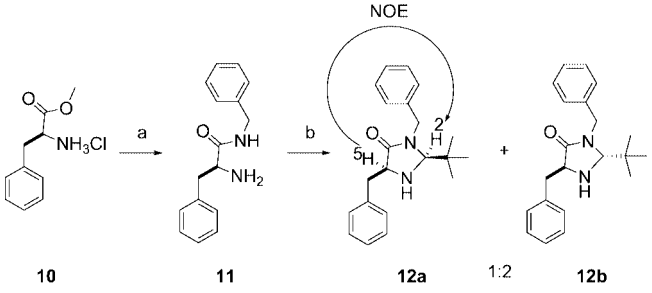
We decided to employ the organocatalysts developed by McMillan[29] in our cycloaddition step. Imidazolidinone catalysts **5**–**9** (Scheme 1) were prepared by published procedures.[29] The stereochemistries of the catalysts **5**–**9** were confirmed by NOE NMR measurements. Cyclization of the amide **8** produced a diastereomeric mixture of imidazolidinones **7a/b** (1:3.1). Unfortunately, the cyclization favored the *trans* cycloadduct. The NOE NMR data showed coupling between the protons 2-H and 5-H in the imidazolidinone ring of **7a**. It was interesting to note that the *cis* product **7a** did not racemize notably during the long reaction time. However, the *trans* product **7b** was prone to racemization, and cycloadduct **7b** was found to be entirely racemic by chiral HPLC analysis.



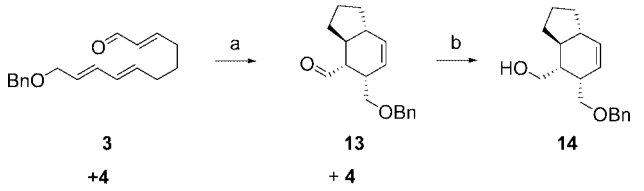
Scheme 1. Reagents and conditions: a) $NaHCO_3$, $CHCl_3$; b) PhCHO, PTSA, MeOH, +75 °C, 4 d (44%).

We also synthesized compound **12**, with an *N*-benzyl group, to test it as a catalyst for this reaction. Thus, (*S*)-phenylalanine methyl ester hydrochloride salt **10** was directly amidated with benzylamine in high yield (88%) (Scheme 2). Cyclization of **11** produced an 18% yield of the correct diastereomer **12a**. The stereochemistry of the catalyst **12a** was confirmed by NOE NMR measurements, protons 2-H and 5-H in the imidazolidinone ring showing NOE. No notable racemization was observed for the *cis* cycloadduct **12a**, but production of the *trans* cycloadduct **12b** was accompanied by racemization.



Scheme 2. Reagents and conditions: a) $BnNH_2$, EtOH, room temp., 23 h (88%); b) $(Me)_3CCHO$, PTSA, MeOH, reflux, 46 h (56%).

The starting materials for the IMDA cycloadditions were mixtures of linear triene aldehyde **3** and the inseparable branched triene aldehyde **4** (Scheme 3). The linear triene aldehyde **3** was more inclined towards polymerization, so some of the experiments were performed with starting materials containing more of the branched triene aldehyde **4**. However, both aldehydes **3** and **4** are capable of forming the iminium ion with the amine catalyst. The catalyst loadings were calculated according to the total aldehyde amount. The branched triene aldehyde **4** resisted cycloaddition and was thus easily separated from the cycloadduct **13** by flash chromatography. The cycloadduct aldehyde **13** was reduced to the corresponding alcohol **14** for analytical purposes.[30] The *endo*/*exo* selectivities were determined by ^1H NMR spectroscopy from the crude product mixtures. The chemical shifts of the formyl protons of the *endo* and *exo* cycloadduct aldehydes **13** differed by about 0.08 ppm.



Scheme 3. Reagents and conditions: a) organocatalyst, solvent mixture, acid; b) $NaBH_4$, EtOH, room temp.

The results of the organocatalytic IMDA cycloadditions are shown in Table 1. Catalyst **8** gave the highest enantioselectivities (Entry 2, 74% *ee*), yields (Entry 3, 99%), and *endo* selectivities (Entries 2, 3, 4, and 7, >99:1) compared to other organocatalysts **7a**, **9**, and **12a**. Trimethyloxazolidinone **9**, which has a stereogenic center only at the C-5 position, was found to give low stereoselectivities (Entry 8), although oxazolidinone **9** is an excellent catalyst for Diels–Alder cycloaddition.[29b] The IMDA cycloaddition of triene aldehyde **3** was observed to be solvent-dependent. Use of a methanol solution afforded somewhat higher enantioselectivity (Entries 2 and 3) than use of an acetonitrile solution, but an extra step was required for cleavage of the acetal formed from the aldehyde **3** during the reaction, and the yield of the cycloadduct **13** was also lower in MeOH than in acetonitrile. The enantioselectivities did not improve significantly at lower temperature (Entries 9 and 10). Furthermore, the low temperature (–20 °C) retarded the reaction significantly, so that it was not complete even after several days. Surprisingly, the enantioselectivity was decreased at lower temperature in the reaction catalyzed by **8** (Entry 3 and 4). This is probably due to racemization of the catalyst during the longer reaction time. In comparison, the enantioselectivity was increased slightly, but the *endo*/*exo* ratio became worse when the reaction was catalyzed by **12a** at low temperature (–20 °C). Although no direct comparison between the acids can be made because the solvent system was also changed, it can be inferred that *p*-toluenesulfonic acid in dichloromethane/propan-2-ol afforded worse *endo*/*exo* selectivities and enantioselectivities than other solvent/acid systems examined (Entries 5 and 11).

Table 1. Conditions and results for the IMDA reaction of the triene aldehyde **3** catalyzed by the organocatalysts **7a**, **8**, **9** and **12a**.

Entry	Catalyst[a]	Substrate (**3**/**4**)	Temperature	Solvent	Acid	*endo*/*exo*[b]	Yield[c] (%)	*ee*[d] (%)
1	**7a**	21:79	room temp.	H_2O/CH_3CN	0.1 M HCl	>99:1	59	10
2	**8**	73:27	room temp.	H_2O/MeOH	0.4 M HCl	>99:1	54	74
3	**8**	21:79	room temp.	H_2O/CH_3CN	0.1 M HCl	>99:1	99[e]	72
4	**8**	65:35	–20 → +6 °C	H_2O/CH_3CN	0.1 M HCl	>99:1	54	66
5	**8**	65:35	–20 → +6 °C	CH_2Cl_2/*i*PrOH	PTSA	25:1	45	41
6	**8**	65:35	–20 → +6 °C	H_2O/THF	TFA	–	–	–
7	**8**[f]	65:35	room temp.	H_2O/CH_3CN	0.1 M HCl	>99:1	79	72
8	**9**	68:32	0 °C → room temp.	H_2O/MeOH	0.4 M HCl	3.3:1	28	–
9	**12a**	65:35	–20 → +6 °C	H_2O/CH_3CN	0.1 M HCl	17:1	40	56
10	**12a**	65:35	room temp.	H_2O/CH_3CN	0.1 M HCl	>99:1	54	47
11	**12a**	65:35	–20 → +6 °C	CH_2Cl_2/*i*PrOH	PTSA	14:1	38	12
12	**12a**	65:35	–20 → +6 °C	H_2O/THF	TFA	–	–	–

[a] 20 mol % of the catalyst relative to the calculated sum of total moles of aldehydes **3** and **4** was used. [b] *endo*/*exo* ratios were determined by ^{1}H NMR from the aldehyde product mixture. [c] Yields of isolated pure aldehydes. The yields were correlated to the amount of linear aldehyde **3** in the beginning of the reaction. [d] For determination of the *ee* values, the aldehyde products were first reduced to alcohols with excess $NaBH_4$ in EtOH, and the resulting alcohols were analyzed by HPLC on a chiral Daicel OD column. Absolute and relative configurations were assigned by chemical correlation to compounds obtained by known methods for Diels–Alder reactions or by analogy. [e] The ratio of the linear triene aldehyde **3** to the branched triene aldehyde **4** in this reaction was 1:3.76. [f] 5.6 mol % of the catalyst was used in this reaction.

Conclusions

A new method to prepare bicyclo[4.3.0]nonane compounds by organocatalysis was found during the development of a route to synthesize amaminol A (**1**). The enantiomer of the bicyclo[4.3.0]nonane substructure of amaminol A (**1**) was synthesized by the novel organocatalytic IMDA cycloaddition to prepare the easily modifiable intermediate aldehyde **13**. It may be possible to synthesize the amaminol A (**1**) substructure as the major product if the IMDA cycloaddition step is catalyzed with the (*R*,*R*)-organocatalyst. Synthesis towards amaminol A (**1**) will be continued and reported on separate report.

Experimental Section

General Remarks: Solvents and starting materials were used as purchased from the suppliers unless otherwise noted. Distilled water was filtered through Millipore filtration system. The glassware was oven-dried (>120 °C) or flame-dried under oil-pump vacuum when dry conditions were required. The reactions were performed under argon when necessary. NMR spectra were recorded with a Varian 400 spectrometer (^{1}H NMR, 399.99 MHz, ^{13}C NMR 100.58 MHz) and a Bruker Avance DPX 400 spectrometer (^{1}H NMR, 400.13 MHz, ^{13}C NMR 100.62 MHz). Thin layer chromatography was performed on silica mesh 60 coated aluminium plates. For visualization, UV light (254 nm) and ninhydrin, phosphomolybdenic acid, anisaldehyde, and permanganate solutions were used. Mass spectra were determined with a JEOL JMS-DX303 apparatus (Helsinki University of Technology) and an LCT Micromass (ES+) (University of Oulu, Department of Chemistry). Flash chromatography was performed with 60 mesh silica. FTIR spectra were measured with a Perkin–Elmer Spectrum One instrument. The melting points were determined with a Gallenkamp MFB-595 apparatus and are not corrected. GC was performed with a Hewlett–Packard 6810 instrument with a Supelco gammadex 120 column, 30 m, 0.25 mm, 0.25 μm film with He as the carrier gas. Gas velocity was 28 cm s^{-1}. An FID detector was used. For chiral HPLC, a Daicel OD column was used (5 × 0.46 cm, 25 × 0.46 cm) with UV detection at λ = 254 nm, and a flow rate of 0.8 mL min^{-1}, unless otherwise noted. The eluent was a mixture of propan-2-ol and hexane.

(2*E*,7*E*,9*E*)-11-Benzyloxyundeca-2,7,9-trienal (3): Crude 11-benzyloxyundeca-2,7,9-trien-1-ol (0.313 g, 1.15 mmol, 100 mol %) was dissolved in CH_2Cl_2 (20 mL), and MnO_2 (0.600 g, 6.9 mmol, 600 mol %) was added. Stirring was continued for 15 h and a second portion of MnO_2 (0.102 g, 1.17 mmol, 102 mol %) was added, and stirring was then continued for another 3.5 h and a third portion of MnO_2 (0.298 g, 3.43 mmol, 298 mol %) was added. Stirring was continued for a further 5 h and the reaction mixture was filtered through a thin pad of Celite and concentrated to give 0.461 g of a yellowish oil. The crude product was purified by flash chromatography (14% MTBE/hexane) to yield **3** (0.264 g, 89% over 2 steps) as a clear oil. R_f (40% MTBE in hexanes) = 0.22. ^{1}H NMR ($CDCl_3$, 400.132 MHz): δ = 9.51 (d, *J* = 7.8 Hz, 1 H), 7.35–7.26 (m, 5 H), 6.83 (dt, *J* = 15.6, 6.8 Hz, 1 H Hz), 6.24 (dd, *J* = 14.8, 10.8 Hz, 1 H Hz), 6.15–6.04 (m, 2 H), 5.75–5.61 (m, 2 H), 4.51 (s, 2 H), 4.05 (d, *J* = 6.0 Hz, 2 H), 2.34 (qd, *J* = 7.3, 1.4 Hz, 2 H Hz), 2.15 (q, *J* = 7.3 Hz, 2 H), 1.62 (q, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ = 194.7, 158.9, 140.8, 139.0, 136.0, 134.4, 133.8, 133.5, 131.2, 129.0, 128.3, 72.7, 71.1, 32.7, 32.6, 28.0 ppm. LRMS (EI+): *m*/*z* (%) = 270, 180, 105, 91 (100), 79, 65. HRMS (EI+): calcd. for [M – 43]: 227.1435; found 227.1491.

(2*S*,5*S*)-5-Benzyl-3-methyl-2-phenylimidazolidin-4-one (7a): The HCl salt of amine **6** (2.37 g, 11.1 mmol, 100 mol %) was treated with a saturated solution of $NaHCO_3$ (45 mL). The free amine was extracted with $CHCl_3$ (3 × 50 mL). The organic layers were dried with Na_2SO_4, filtered, and concentrated to give 2.05 g of a yellowish oil. Methanol (20 mL), benzaldehyde (1.29 g, 12.2 mmol, 110 mol %), and *para*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol, 10 mol %) were added, and the reaction mixture was warmed with an oil bath to +75 °C. Stirring was continued for 3 d and the reaction mixture was allowed to cool to room temp. The solvents were evaporated to give 3.26 g of an orange oil. The crude product was purified by flash chromatography (50–100% EtOAc/hexane) to yield **7a** (0.31 g, 11%) as a yellowish oil. The ratio of (*S*,*S*)/(*S*,*R*/*R*,*S*) products was 1:3.1 by ^{1}H NMR spectroscopy. R_f (*S*,*S*) (75% EtOAc in hexanes) = 0.16. $[\alpha]_D^{20}$ = –46.5 (*c* = 1.12, $CHCl_3$). R_f (*S*,*R*/*R*,*S*) (75% EtOAc in hexanes) = 0.33. The product was analyzed by chiral HPLC (10% *i*PrOH in hexane, flow rate 1.0 mL min^{-1}) The retention times were 13.59 min for (*S*,*S*) and

11.8 min for (*S*,*R*); the retention time for (*R*,*S*) was 9.4 min. ^{1}H NMR ($CDCl_3$, 400.132 MHz): δ = 7.32–7.24 (m, 8 H), 6.85–6.83 (m, 2 H), 5.14 (d, *J* = 1.5 Hz, 1 H), 3.88 (t, *J* = 0.5 Hz, 1 H), 3.28–3.16 (m, 2 H), 2.56 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ = 174.4, 138.4, 136.7, 129.8, 129.5, 129.0, 128.8, 127.1, 126.9, 77.6, 60.4, 36.8, 27.3 ppm. HRMS (ES+): calcd. for [M + 1] ($C_{17}H_{19}N_2O$): 267.1497; found 267.1484.

(2*S*,5*S*)-3,5-Dibenzyl-2-*tert*-butylimidazolidin-4-one (12a): Free amine **11** (2.22 g, 8.73 mmol, 100 mol %) was dissolved in MeOH (15 mL). Trimethylacetaldehyde (0.83 g, 9.60 mmol, 110 mol %) and *para*-toluenesulfonic acid monohydrate (0.17 g, 0.87 mmol, 10 mol %) were added. The resulting mixture was warmed with an oil bath to +75 °C. Stirring was continued under reflux for 2 d and the reaction mixture was allowed to cool to room temp. The solvents were evaporated to give 2.72 g of a yellow oil. The crude product was purified by flash chromatography (32% EtOAc/hexane) to yield **12a** (0.52 g, 18%) as a clear oil. The ratio of (*S*,*S*)/(*S*,*R*/*R*,*S*) was 1:2 by ^{1}H NMR spectroscopy. R_f (*S*,*S*) (70% EtOAc/hexane) = 0.49. $[\alpha]_D^{20}$ = –128.0 (*c* = 1.11, $CHCl_3$). R_f (*S*,*R*/*R*,*S*) (70% EtOAc/hexane) = 0.65. ^{1}H NMR ($CDCl_3$, 400.132 MHz): δ = 7.32–7.13 (m, 10 H), 5.06 (d, *J* = 15.7, 1 H), 4.25 (d, *J* = 15.7 Hz, 1 H), 4.13 (s, 1 H), 3.85 (ddd, *J* = 7.5, 4.1, 1.4 Hz, 1 H), 3.22 (dd, *J* = 13.7, 4.1 Hz, 1 H), 3.04 (dd, *J* = 13.7, 7.5 Hz, 1 H), 0.76 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ = 174.4, 138.4, 136.7, 129.8, 129.5, 129.0, 128.8, 127.1, 126.9, 77.6, 60.4, 36.8, 27.3 ppm. The (*S*,*S*) configuration was confirmed by COSYGPGF (coupling between δ = 4.13 and 3.85 ppm was observed). HRMS (EI): calcd. for $C_{21}H_{26}N_2O$: 322.2045; found 321.1994 for [M – 1].

(3a*S,4*R**,5*S**,7a*R**)-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (13):** (2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (**8**, 128 mg, 0.52 mmol, 6 mol %) was dissolved in CH_3CN (20 mL) and an aqueous solution of HCl (0.1 M, 5.2 mL) was added. The resulting mixture was stirred for 5 min and triene aldehyde **3** (65 wt %, 2.50 g, 9.25 mmol, 100 mol %) in CH_3CN (32 mL) was added. The reaction mixture was stirred for 20 h and diluted with diethyl ether (200 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated to give 2.8 g of a yellow oil. The crude product was purified by flash chromatography (5% EtOAc/hexane) to give **13** (1.23 g, 79%, 72% *ee*) as a clear oil. The branched triene aldehyde **4** was easily separated by flash chromatography. The enantiomeric excess was determined by chiral HPLC from the corresponding alcohol **14**. R_f (20% MTBE in hexanes) = 0.34. $[\alpha]_D^{20}$ = +23.3 (*c* = 1.33, $CDCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz): δ = 9.77 (d, *J* = 2.8 Hz, 1 H), 7.34–7.27 (m, 5 H), 5.96 (d, *J* = 9.9 Hz, 1 H), 5.47 (ddd, *J* = 9.9, 3.9, 2.6 Hz, 1 H), 4.41 (d, *J* = 11.6 Hz, 1 H), 4.33 (d, *J* = 11.6 Hz, 1 H), 3.44 (dd, *J* = 9.9, 3.6 Hz, 1 H), 3.37 (t, *J* = 9.4 Hz, 1 H), 3.09 (m, 1 H), 2.61 (ddd, *J* = 11.6, 6.5, 2.7 Hz, 1 H), 2.06 (m, 1 H), 1.84–1.61 (m, 5 H), 1.17–1.04 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ = 203.2, 137.7, 132.3, 128.4, 127.8, 127.7, 126.2, 72.8, 70.7, 55.3, 45.0, 39.8, 39.6, 28.4, 27.6, 22.4 ppm. LRMS (EI+): *m*/*z* (%) = 270, 180, 105, 91 (100), 79, 65. HRMS (EI): calcd. for $C_{18}H_{22}O_2$: 270.1620; found 270.1624.

(3a*S,4*R**,5*S**,7a*R**)-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)methanol (14):** The cyclic aldehyde **13** (9 mg, 0.033 mmol, 100 mol %) was dissolved in EtOH (1 mL), and $NaBH_4$ (excess) was added at room temp. The reaction mixture was stirred for 1 h and quenched with aqueous citric acid (5 wt %, 1 mL). The product was extracted with diethyl ether (3 × 2 mL) and washed with brine (2 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated to give **14** (9.3 mg) as a clear oil. R_f (40% MTBE in hexanes) = 0.35. UV: λ(max) = 239 nm. HPLC (5% *i*PrOH in hexanes). The retention time of the minor diastereomer was 11.4 min, and of the major diastereomer 13.7 min. The enantiomeric excess was 72%. $[\alpha]_D^{20}$ = +92.5 (*c* = 0.32, MeOH). ^{1}H NMR ($CDCl_3$, 400.132 MHz): δ = 7.33 (m, 5 H), 5.90 (d, *J* = 9.8 Hz, 1 H), 5.45 (ddd, *J* = 9.6, 4.3, 2.4 Hz, 1 H), 4.52 (s, 2 H), 3.67–3.51 (m, 4 H), 3.35 (dd, *J* = 9.6, 1.7 Hz, 1 H), 2.84 (m, 1 H), 2.02 (m, 1 H), 1.80–1.68 (m, 6 H), 1.22–1.08 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100.62 MHz): δ = 137.2, 132.2, 128.6, 128.1, 128.0, 127.4, 73.6, 71.2, 63.2, 46.1, 44.5, 41.7, 38.7, 28.7, 27.1, 22.5 ppm. HRMS (EI): calcd. for $C_{18}H_{24}O_2$: 272.1776; found 272.1786.

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