Synthesis of optically active benzocyclobutene and biphenylene based unusual α-amino acid derivatives

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Optically active benzocyclobutene and biphenylene based unusual α-amino acid derivatives have been prepared via a six step sequence using Schöllkopf chiral auxiliary in a very high diastereoselective manner.

Benzocyclobutene 1 (BCB) and its derivatives represent a unique class of reactive molecules because of thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring. They are useful building blocks in organic synthesis because of their ability to isomerize to o-xylene upon thermal activation (Eqn 1). The temperature required for electrocyclic ring opening reaction depends on the nature of substituents on the cyclobutene moiety. o-Xylene 2 can be trapped by various dienophiles in Diels-Alder fashion either by intermolecular or intramolecular process (Eqn 2). This strategy has been used in the literature to construct various polycyclic and heterocyclic systems. Recently BCBs are also used to prepare conducting polymers and crosslinking agents. Several BCB derivatives are used to functionalize C60. 1-Benzocyclobutene glycine and similar derivatives were synthesized in connection with CNS depressants. In view of diverse applications of BCBs in organic synthesis and polymer synthesis it occurred to us that amino acids containing BCB unit (e.g. 3-6) may provide an unique opportunity for post-translational peptide modifications via the Diels-Alder methodology. Here we describe the full details for the preparation of various optically pure BCB based α-amino acid (AAA) derivatives related to 3.7

Retrosynthetic analysis of 3 indicates (Figure 1) eight viable routes for its preparation. Strategically these routes can be classified into four categories. In the first category the phenylalanine derivatives can be extended to the required BCB derivative 3 by selective C-C bond formation reactions (path a and b) or via benzene intermediate (path c). The second strategy involves cyclobutene derivatives as starting materials and the benzene ring is constructed by cycloaddition approach (path f and g). Alternatively, both benzene and cyclobutene moieties can be assembled via a [2+2+2] cycloaddition approach as shown in path e. Finally, 3 can be prepared starting with preformed benzocyclobutene system (path d and h). Path d can be realized by replacing hydroxy group of serine with suitably substituted BCB derivatives. The other route...
(path h) involves asymmetric derivatization of glycine derivative with BCB moiety.

Since asymmetric derivatization of glycine is well known in the literature, we have chosen path h in the present study. The required bromo derivative 9 was prepared in a four-step sequence starting from α-chloro-o-xylene as shown in Scheme I. Thus, flash vacuum pyrolysis of α-chloro-o-xylene at 780°C (0.3 mm/Hg) gave the benzocyclobutene contaminated with the starting material, which was treated with the excess amount of powdered KOH in presence of DMSO to eliminate the starting material and then usual work up and distillation under reduced pressure gave the pure BCB. Under Viisheimer formylation conditions (POCl₃/DMF), BCB did not give the required aldehyde. However, formylation of 1 with Cl₂CHOME in presence of TiCl₄ in dry dichloromethane at 0°C gave the required aldehyde 7 in 34% yield.

Reduction of the aldehyde 7 was achieved by treatment with NaBH₄ in presence of dry methanol at 0°C to give hydroxy derivative 8 (85% yield, mp 59-60°C). Conversion of hydroxy compound 8 to the corresponding bromo derivative 9 proved to be more difficult than anticipated. Initial attempts to prepare bromo derivative 9 under PBr₃/ether/pyridine conditions gave the ring-opened product along with minor amount of the bromo derivative 9. Later on, attempts to prepare the tosyl derivative from 8 under various reaction conditions were unsuccessful. After considerable amount of experimentation, we found that treatment of hydroxy derivative 8 with NaBr/BF₃.OEt₂ in acetonitrile at 0°C gave the bromo derivative 9 in 70% isolated yield as a low melting solid. Then, the bromo derivative 9 was treated with mono-anion of Schöllkopf’s bis-lactim ether 12a at −78°C and the reaction mixture was quenched with water to give 10 in 75% yield after silica gel flash column chromatography. The diastereoselectivity of the C-C bond formation step is very high. During the purification of 10 we were able to isolate the minor diastereomer in an impure form (≤2%). The structure of 10 was in full agreement with its spectral data. The IR spectrum of 10 showed a strong absorption at 1694 cm⁻¹ due to C=N stretching. In the ¹H NMR spectrum two doublets at δ 0.61, and 0.95 (2d, J=6.9 Hz) are due to two methyl groups of CHMe₂. The two singlets at δ 3.68 and 3.71 are due to two methoxy groups.
The 18-line $^{13}$C NMR spectrum of 10 resonating at $\delta$ 16.5, 19.1, 29.2, 29.4, 31.3, 40.6, 52.2, 52.4, 56.9, 60.3, 121.8, 124.1, 128.6, 135.9, 143.6, 145.2, 162.7, 163.8 delineated its structure. The mass spectrum at m/z 300 amu for C$_{18}$H$_{24}$N$_{2}$O$_{2}$ further supported molecular formulation of 10. Two other chiral auxiliaries (12b and 12c) were alkylated with bromo derivative 9 to give the corresponding coupling products 13 and 14 (Table 1). All the products were characterized on the basis of spectral data.

It is well known in the literature that electrophile enters from the opposite side of the isopropyl group during alklylation step. The homogeneity of the major diastereomer formed here has been established by $^{13}$C NMR spectral data. Hydrolysis of 10 with 0.1 N HCl at RT gave the amino ester 11. The structure of 11 was fully established on the basis of spectral data. The IR spectrum showed absorption bands at 3378 and 1737 cm$^{-1}$ due to amine and ester functional groups respectively. The $^1$H NMR spectrum with three singlets at $\delta$ 2.13, 3.13 and 3.72 due to amine, cyclobutene ring and ester methyl groups respectively. It exhibited a part of a doublet of 1/2 ABq at $\delta$ 2.82 ($J$=8, 13.5 Hz) and another part of a doublet of 1/2 ABq at $\delta$ 3.08 ($J$=8, 13.5 Hz) due to diastereotopic protons. The multiplet at $\delta$ 3.70 is due to $\alpha$ proton. The 12-lines in $^{13}$C NMR (δ 29.3, 29.4, 41.4, 52.0, 55.9, 122.6, 123.4, 127.9, 135.5, 144.3, 146.1, 175.3) supported the structure of 11. The molecular ion peak in the mass spectrum at m/z 205 (C$_{12}$H$_{15}$NO$_{2}$) confirmed the structural formulation of 11. Two other alkylated products 13 and 14 were hydrolyzed under similar reaction conditions to give the amino ester derivatives 15 and 16 (Table 1), verifies the generality of this method.

**Biphenylene-based unusual $\alpha$-amino acid derivatives**

Biphenylene (BP) 17 is dibenzo derivative of cyclobutadiene 18 having 4π electrons and expected to show anti-aromatic behavior. BP is normally stable and behave like aromatic compound. BP has five canonical or Kekule forms in which the structure 17 represents the purely covalent form. BP 17 is a unique molecule because of the presence of a formal cyclobutadiene unit. In the beginning, ring structure, reactivity, and other properties are the major driving forces for the development of BP chemistry.

Recently, several derivatives of 17 have been prepared and found interesting applications in chemical sciences. For example, Su and co-workers have shown that BP containing monomer unit could be smoothly converted into a highly conjugated polymer under electrochemical oxidation conditions. BP-based bidentate ligands are known to accelerate the Diels-Alder reactions, and also improve the
selectivity of Mukaiyama aldol reactions. In addition, BP is anticipated as a unit of new carbon allotropes.

In view of various applications of BP and its derivatives, we are interested in preparing the corresponding AAA derivatives related to 19 and 20. Retrosynthetic analysis of 19 (Figure 2) indicates seven possible routes for its assembly. Path a involves formation of C-C bond in biphenyl derivative possibly by Ullmann coupling reaction. The second route (path b) relies on construction of two C-C bonds via benzene intermediates. Cycloaddition reaction is the key step in the other three routes (path c, d, and e). The remaining two routes (path f and g) involve preformed BP unit as the starting material. Due to its simplistic nature, we have selected path g involving asymmetric derivatization of glycine with suitably substituted BP derivative.

The required BP 17 was prepared by dimerization of benzene 22. Thus, diazotization of anthranilic acid 21 in presence of isomyl nitrite and trifluoroacetic acid gave benzenediazonium-2-carboxylate (all diazonium salts must be handled with proper safety precautions) which was converted into BP 17 in boiling 1,2-dichloroethane.\(^\text{20}\) Formylation of BP 17 with \(\alpha,\alpha\)-dichloromethyl methyl ether in presence of titanium(IV)chloride gave 2-formylbiphenylene 23 in 73% isolated yield after column chromatography.\(^\text{21}\) Reduction of 23 with sodium borohydride at 0°C gave the alcohol 24 in 87% yield after silica gel flash column chromatography (Scheme II). The IR spectrum of 24 showed a broad absorption band at 3337 cm\(^{-1}\) due to hydroxyl group. The alcohol 24 on treatment with phosphorus tribromide in benzene gave bromo derivative 25 in quantitative yield. The structure of 25 was characterized by its spectral data. The IR spectrum showed the absence of peak at 3337 cm\(^{-1}\), describe the conversion of alcohol to
bromo derivative. The $^1$H NMR spectrum displayed a singlet at $\delta$ 4.30 due to benzylic protons, and a multiplet at $\delta$ 6.54-6.62 due to aromatic protons. Reaction of mono-anion of Schöllkopf's bis-lactim ether (2R)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine $12a$ with bromo derivative $25$ at $-78$ °C gave $26$ in 74% yield after purification. TLC and $^{13}$C NMR data indicated that the minor diastereomer was not present during the alkylation reaction. The structure of $26$ was confirmed by its complementary spectral data. The IR absorption at 1686 cm$^{-1}$ describe the presence of (C=N). In the $^1$H NMR spectrum two doublets at $\delta$ 0.63 and 0.99 (2d, $J$=6.9 Hz) due to two methyl groups of CHMe$_2$. The two singlets at $\delta$ 3.68
Table II — Coupling (26, 28) and hydrolysis (27, 29) products from 12a and 12b

<table>
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<th>Sl. No.</th>
<th>Chiral auxiliary</th>
<th>Coupling product</th>
<th>Yield (%)</th>
<th>Hydrolysis product</th>
<th>Yield (%)</th>
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<td>28</td>
<td>75</td>
<td>29</td>
<td>95</td>
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and 3.71 are due to the presence of two methoxy groups. The 21-line $^{13}$C NMR spectrum of 26 [δ 16.4, 16.6, 19.1, 31.3, 40.5, 52.2 (2C?), 56.5, 60.4, 117.0, 117.1, 119.6, 127.9, 128.1, 129.3, 137.8, 149.3, 150.8, 151.3, 162.4, 164.0] delineated its structure. The high-resolution mass spectrum at m/z at 348.1837 amu further supported its molecular formulation (C$_{22}$H$_{24}$N$_2$O$_2$).

Similarly, alkylation reaction was carried out with other Schöllkopf's bis-lactim ether 12b to give the corresponding alkylated product 28 (Table II). All the products were characterized with appropriate spectral data, and the details are included in the experimental section. Hydrolysis of 26 with 0.1 N HCl in diethyl ether gave the amino ester 27, whose structure was in full agreement with its spectral data. The IR spectrum showed the absorption bands at 3407 and 1740 cm$^{-1}$ due to amine and ester functional groups respectively. In the $^1$H NMR spectrum a broad singlet at δ 1.76 due to amine group, and the two diastereotopic protons appeared at δ 2.65 (d of 1/2 ABr $J$=7.6, 13.5 Hz) and 2.88 (d of 1/2 ABr $J$=7.6, 13.5 Hz). The α proton appears at δ 3.67 (dd, $J$=5.4, 7.8 Hz). The singlet at δ 3.73 is due to ester methyl group and also the spectrum showed a multiplet at δ 6.50-6.74 due to aromatic protons. $^{13}$C NMR spectrum [δ 29.7, 41.6, 52.1, 55.6, 117.3, 117.5, 118.6, 128.2, 128.4, 128.7, 137.4, 149.8, 151.0, 151.8, 175.4] further supported the structure of 27. The structure of 27 was also confirmed by its mass spectral data with molecular ion peak at 253 amu (C$_{16}$H$_{15}$NO$_2$).

Similarly hydrolysis of 28 gave the amino ester 29 (Table II). During the alkylation reaction of Schöllkopf's bis-lactim ether 12c with bromo derivative 25 gave the alkylated product, but in hydrolysis step gave a mixture of amino ester and dipeptide and we were unable to separate the two compounds.

In conclusion, we have shown that NaBr/BF$_3$OEt$_2$ in acetonitrile protocol has been found to be useful for ROH to RBr transformation where cyclobutene ring system is involved. For the first time, we have prepared optically pure BCB-based and BP-based AAA derivatives using Schöllkopf chiral auxiliary in good yield. The generality of the method has been demonstrated with two other chiral auxiliaries. Since benzo-cyclobutene derivatives and amino acids with unusual side chains have many applications in organic synthesis and peptide modifications, the unusual AAA derivatives prepared here may find useful applications in bioorganic and medicinal chemistry.

**Experimental Section**

Flash vacuum pyrolysis was carried out with home made quartz pyrolysis equipment. BF$_3$OEt$_2$ was dried over CaH$_2$ and then distilled at reduced pressure under
inert atmosphere. Dry diethyl ether and THF were obtained by distillation over benzenophenone ketyl. Schöllkopf chiral auxiliaries were purchased from Merck Schuchardt Ltd.

(2S, 5R) 2-Benzocyclobutene-3-ylmethyl-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine 10. To a stirred solution of Schöllkopf chiral auxiliary (2R)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 12a (134 mg, 0.73 mmole) in dry THF (3 mL) was added 1.6 M solution of n-BuLi (0.45 mL, 0.73 mmole) at −78 °C and stirred for 1.25 hr. Then, the bromo derivative 9 (143 mg, 0.73 mmole) in dry THF (2 mL) was added slowly over a period of 3 min and stirred at the same temperature for 4 hr and the reaction mixture was brought to RT and stirred for another 1.5 hr. The reaction mixture was quenched with water (1 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over MgSO₄. Evaporation of the solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 5% ethyl acetate/petroleum ether mixture gave alkylated product 13 (63 mg, 69%) as a semi solid. IR (neat) 1694 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.61, 0.95 (2d, J=6.7 Hz, 6H), 2.12-2.19 (m, 1H), 3.04 (dd, J=3.6 Hz, J=4.8 Hz, 2H), 3.09 (s, 4H), 3.37 (t, J=3.4 Hz, 1H), 3.67, 3.71 (2s, 6H), 4.27 (dd, J=5.1 Hz, J=8.7 Hz, 1H), 6.80 (s, 1H), 6.86-6.93 (m, 2H); ¹³C NMR (75.4 MHz, CDCl₃): δ 16.5, 19.1, 29.2, 29.4, 31.3, 40.6, 52.1, 52.4, 56.9, 60.3, 121.8, 124.1, 128.6, 135.9, 143.6, 145.2, 162.7, 163.8; Mass: m/z 300 (M⁺); HRMS: m/z (EI) for C₁₈H₂₄N₂O₂ (Calcd: 300.1837; Found: 300.1837); [α] D 20.99 (c 1, EtOH).

Synthesis of (2S, 5R) 2-Benzocyclobutene-3-ylmethyl-5-isopropyl-3,6-dimethoxy-2-methyl-2,5-dihydro-pyrazine 14. To a stirred solution of Schöllkopf chiral auxiliary (2R)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methyl pyrazine 12c (62 mg, 0.31 mmole) in dry THF (2 mL) was added 1.5 M solution of n-BuLi (0.20 mL, 0.31 mmole) at −78 °C and stirred for 1.5 hr. Then the bromo derivative 9 (62 mg, 0.31 mmole) in dry THF (2 mL) was added slowly over a period of 3 min and stirred at the same temperature for 4 hr. Then the reaction mixture was brought to RT and stirred for another 1.5 hr and quenched with water (1 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over MgSO₄. Evaporation of the solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 2% ethyl acetate/petroleum ether mixture gave starting material (15 mg) and alkylated product 14 (53 mg, 74% based on starting material recovered). IR (neat) 1693 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.60, 0.95 (2d, J=6.9 Hz, 6H), 1.44 (s, 3H), 2.07-2.16 (m, 1H), 2.74 (d, J=12.8 Hz, 2H), 3.07 (s, 4H), 3.28 (d, J=3.3 Hz, 1H), 3.66, 3.68 (2s, 6H), 6.71 (s, 1H), 6.84 (d, J=0.91 Hz, 2H); ¹³C NMR (75.4 MHz, CDCl₃): δ 16.7, 19.2, 28.6, 29.2, 30.3, 30.7, 48.0, 51.9, 52.1, 59.9, 60.6, 121.8, 124.2, 128.6, 136.1, 143.5, 144.9, 161.8, 164.3; Mass: m/z 314 (M⁺); [α] D +18.1 (c 1, EtOH); HRMS: m/z (EI) for C₁₉H₂₅N₂O₂ (Calcd: 314.1994; Found: 314.2009).

(5)-2-Amino benzocyclobutene-3-yl-propionic acid methyl ester 11. To a stirred solution of the coupling product 10 (53 mg, 0.176 mmole) in diethyl ether (2 mL) was added 1N HCl (1 mL) and stirred for 12 hr at RT. Then, the aq. layer was separated and purification was performed by flash column chromatography.
washed with diethyl ether to remove unwanted organic residues. The aq. phase was brought to pH=10 with ammonia solution and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over MgSO₄. Evaporation of solvent gave amino ester 11 (35 mg, 97%) as a sticky solid. IR (KBr): 3370, 1737 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.13 (br s, 2H), 2.82 (d of 1/2 ABq, J=8.0 Hz, J=13.5 Hz, 1H), 3.08 (d of 1/2 ABq, J=8.0 Hz, J=13.5 Hz, 1H), 3.13 (s, 4H), 3.70 (m, 1H), 3.72 (s, 3H), 6.89 (s, 1H), 6.92-6.98 (m, 2H); ¹³C NMR (75.4 MHz, CDCl₃): δ 29.3, 29.4, 41.4, 52.0, 55.9, 122.6, 123.4, 127.9, 135.5, 144.3, 146.1, 175.3; Mass: m/z 205 (M⁺); [α] D 9.9 (c 0.42, EtOH).

(R)-2-Amino benzocyclobuten-3-yl-propionic acid methyl ester 15. To a stirred solution of the coupling product 13 (70 mg, 0.233 mmole) in diethyl ether (3 mL) was added 1N HCl (1 mL) and stirred for 24 hr at RT. Then the aqueous layer was separated and washed with diethyl ether to remove unwanted organic residues. The aqueous phase was brought to pH=10 with ammonia solution and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over MgSO₄. Evaporation of solvent gave amino ester 15 (45 mg, 94%) as a sticky solid. IR (KBr): 3370, 1738 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.13 (br s, 2H), 2.82 (d of 1/2 ABq, J=8.0 Hz, J=13.5 Hz, 1H), 3.08 (d of 1/2 ABq, J=8.0 Hz, J=13.5 Hz, 1H), 3.13 (s, 4H), 3.70 (m, 1H), 3.72 (s, 3H), 6.89 (s, 1H), 6.92-6.98 (m, 2H); Mass: m/z 205 (M⁺); [α] D 10.18 (c 0.6, EtOH).

(S)-2-Aminobenzocyclobuten-3-yl-2-methyl-propionic acid methyl ester 16. To a stirred solution of the coupling product 14 (53 mg, 0.168 mmole) in diethyl ether (3 mL) was added 1N HCl (1 mL) and stirred for 24 hr at RT. Then the aqueous layer was separated and washed with diethyl ether to remove unwanted organic residues. The aq. phase was brought to pH=10 with ammonia solution and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over MgSO₄. Evaporation of solvent gave amino ester 16 (36 mg, 97%) as a sticky solid. IR (KBr): 3374, 1738 cm⁻¹; ¹H NMR (300 MHz, acetone d₆): δ 2.05 (s, 3H), 2.73 (d, J=13.0 Hz, 2H), 2.95 (br s, 2H), 3.08 (s, 4H), 3.63 (s, 3H), 6.85-6.95 (m, 3H); Mass: m/z 219 (M⁺); [α] D 2.33 (c 1, EtOH).

2-Hydroxymethyl biphenylene 24. Sodium borohydride (80 mg, 2.11 mmole) was added to the solution of 23 (183 mg, 1.01 mmole) in dry methanol (15 mL). The reaction mixture was kept under N₂ and stirred at RT for 1 hr. Then, the reaction mixture was quenched with water (5 mL) and the solvent was removed under reduced pressure. The reaction mixture was diluted with water and extracted with ethyl acetate (25 mL × 3). The organic layers were combined and washed with water (25 mL), brine (25 mL) and dried over MgSO₄. The solvent was removed on a rotary evaporator, and crude product was purified by silica gel flash column chromatography. Elution of the column with 10% ethyl acetate/petroleum ether mixture gave 24 as a light yellow solid (160 mg, 87%). m.p. 112-13 °C; IR (KBr): 3337 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.55 (brs, 1H) 4.46 (d, J=5.8 Hz, 2H), 6.58-6.78 (m, 7H); ¹³C NMR (125 MHz, CDCl₃): δ 65.9, 116.9, 117.2, 117.6, 117.7, 126.7, 128.5, 128.6, 141.2, 150.9 (2C⁺), 152.0; Mass: m/z 182 (M⁺); Anal. Found: C, 85.36; H, 5.40. C₁₃H₁₀O requires C, 85.69; H, 5.53%.

2-Bromomethyl biphenylene 25. Phosphorous tribromide (0.6 mL, 6.38 mmole) was added to the solution of 24 (120 mg, 0.66 mmole) in dry benzene (10 mL). The reaction mixture was kept under N₂ and stirred at RT for one day. Then, the reaction mixture was quenched with water (2 mL) and benzene was evaporated on a rotary evaporator. The reaction mixture was extracted with diethyl ether (25 mL × 3). The organic layers were combined and washed with water (25 mL), brine (25 mL) and were dried over MgSO₄. The solvent was removed on a rotary evaporator to give a yellow solid. Recrystallization of the product from petroleum ether gave 25 (161 mg, quantitative yield). m.p 106-07 °C; IR (KBr): 3300-3200 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.40 (s, 2H), 6.54-6.82 (m, 7H). Anal. Found: C, 63.34; H, 3.69. C₁₃H₁₀Br requires C, 63.67; H, 3.67%.

(2S, 5R)-2-Biphenyl-2-ylmethyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine 26. To a stirred solution of Schöllkopf chiral auxiliary (2R)−(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 12a (25 mg, 0.135 mmole) in dry THF (3 mL) was added 1.6 M solution of n-BuLi (0.09 mL, 0.14 mmole) at −78°C and stirred for 1 hr. Then, the 2-bromomethyl biphenylene 25 (33 mg, 0.135 mmole) in dry THF (2 mL) was added slowly over a period of 3 min and stirred at the same temperature for 3 hr. The reaction mixture was brought to RT and stirred for another 2 hr, quenched with water (1 mL) and extracted with
ethyl acetate (25 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over MgSO_4. Evaporation of the solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 5% ethyl acetate/petroleum ether mixture gave alkylation product 26 as a sticky solid (35 mg, 74%). UV(CHCl_3): λ_{max} (ε M^{-1} cm^{-1}) 363.5 (8.25 x 10^3), 345.5 (5.98 x 10^3), 253.5 (5.50 x 10^3) nm; IR (neat): 1686 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ 0.63, 0.99 (2d, J=6.9 Hz, 6H), 2.17-2.23 (m, 1H), 2.88 (d, J=5.1 Hz, 2H), 3.61 (t, J=3.6 Hz, 1H), 3.68, 3.71 (2s, 6H), 4.25 (dd, J_p=4.7 Hz, J_A=8.8 Hz, 1H), 6.41-6.73 (m, 7H). ^13C NMR (75.4 MHz, CDCl_3): δ 16.4, 16.6, 19.1, 31.3, 40.5, 52.2, 56.5, 60.4, 117.0, 117.1, 119.6, 127.9, 128.1, 129.3, 137.8, 149.3, 150.8, 151.3, 162.4, 164.0. HRMS: m/z (EI) for C_{27}H_{24}N_2O_2 (Calcd: 346.0; Found: 345.5). [α]_D^20 +10.26 (c 0.8, EtOH).

(2R, 5S)-2-Biphenylene-2-ylmethyl-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine 28. To a stirred solution of Schöllkopf chiral auxiliary (25)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine 12b (32 mg, 0.173 mmol) in dry THF (3 mL) was added 1.5 M solution of n-BuLi (0.11 mL, 0.173 mmol) at -78°C and stirred for 1 hr. Then, the 2-bromomethyl biphenylene 25 (42.5 mg, 0.173 mmol) in dry THF (2 mL) was added slowly over a period of 3 min and stirred at the same temperature for 3 hr. The reaction mixture was brought to RT and stirred for another 2 hr, quenched with water (1 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over MgSO_4. Evaporation of the solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 5% ethyl acetate/petroleum ether mixture gave the starting material 25 (10 mg) and alkylation product 28 as a light yellow solid (34 mg, 75%, based on starting material recovered 10 mg). m.p.: 42-43°C; UV (CHCl_3): λ_{max} (ε M^{-1} cm^{-1}) 363.0 (3.10 x 10^3), 346.0 (2.21 x 10^3), 253.5 (1.95 x 10^3) nm; IR (neat): 1694 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ 0.63, 0.99 (2d, J=6.9 Hz, 6H), 2.17-2.25 (m, 1H), 2.88 (d, J=4.7 Hz, 2H), 3.61 (t, J=3.3 Hz, 1H), 3.67, 3.71 (2s, 6H), 4.25 (dd, J_p=4.7 Hz, J_A=8.8 Hz, 1H), 6.41-6.73 (m, 7H). ^13C NMR (75.4 MHz, CDCl_3): δ 16.4, 16.5, 19.1, 31.3, 40.5, 52.2, 56.5, 60.4, 116.9, 117.0, 117.1, 119.6, 127.9, 128.1, 129.3, 137.8, 149.3, 150.8, 151.3, 162.4, 164.0. HRMS: m/z (EI) for C_{27}H_{24}N_2O_2 (Calcd: 348.1837. Found: 348.1837); [α]_D^20 +13.36 (c 1.6, EtOH).

(5S)-2-Amino-3-biphenylene propionic acid methyl ester 27. To a stirred solution of the coupling product 26 (25 mg, 0.071 mmole) in diethyl ether (3 mL) was added 1N HCl (1 mL) and stirred for 24 hr at RT. Then, the aq. layer was separated and washed with diethyl ether to remove unwanted organic residues. The aq. phase was brought to pH ~10 with ammonia solution and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over MgSO_4. Evaporation of solvent gave amino ester 27 (17 mg, 94%) as a sticky solid. IR (KBr): 3407, 1740; UV (CHCl_3): λ_{max} (ε M^{-1} cm^{-1}) 363.5 (5.41 x 10^3), 346.0 (4.05 x 10^3), 252.0 (3.00 x 10^3) nm; ^1H NMR (300 MHz, CDCl_3): δ 1.76 (br s, 2H), 2.65 (d of 1/2 AB q, J_p=6.7 Hz, J_A=13.5 Hz, 1H), 2.88 (d of 1/2 AB q, J_p=7.6 Hz, J_A=13.5 Hz, 1H), 3.67 (dd, J_p=5.4 Hz, J_A=7.8 Hz, 1H), 3.73 (s, 3H), 6.50-6.74 (m, 7H). ^13C NMR (75.4 MHz, CDCl_3): δ 29.7, 41.6, 52.1, 55.6, 117.3, 117.5, 118.6, 128.2, 128.4, 128.7, 137.4, 149.8, 151.0, 151.8, 175.4; Mass: m/z 253 (M); [α]_D^20 +10.26 (c 0.8, EtOH).

(R)-2-Amino-3-biphenylene propionic acid methyl ester 29. To a stirred solution of the coupling product 28 (20 mg, 0.057 mmole) in diethyl ether (3 mL) was added 1N HCl (1 mL) and stirred for 24 hr at RT. Then the aq. layer was separated and washed with diethyl ether to remove unwanted organic residues. The aq. phase was brought to pH ~10 with ammonia solution and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with water (15 mL), brine (15 mL) and dried over MgSO_4. Evaporation of solvent gave amino ester 29 (14 mg, 95%) as a sticky solid. UV (CHCl_3): λ_{max} (ε M^{-1} cm^{-1}) 363.0 (4.40 x 10^3), 346.0 (3.26 x 10^3), 253.0 (2.56 x 10^3) nm; IR (KBr): 3372, 1739 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ 1.62 (br s, 2H), 2.65 (d of 1/2 AB q, J_p=7.6 Hz, J_A=13.5 Hz, 1H), 2.88 (d of 1/2 AB q, J_p=7.6 Hz, J_A=13.5 Hz, 1H), 3.67 (dd, J_p=5.4 Hz, J_A=7.8 Hz, 1H), 3.73 (s, 3H), 6.50-6.74 (m, 7H); Mass: m/z 253 (M); [α]_D^20 +8.61 (c 0.8%, EtOH).

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References and Notes


