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FIRST SYNTHESIS OF OPTICALLY ACTIVE BENZOCYCLOBUTENE AND BIPHENYLENE-BASED UNUSUAL α-AMINO ACID DERIVATIVES[1]

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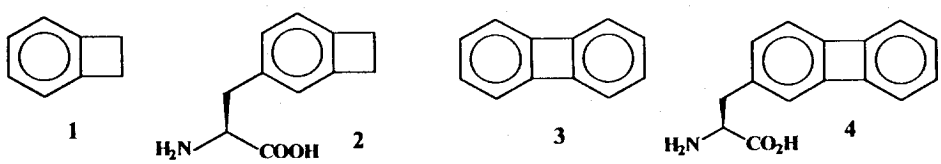
Abstract: Various optically pure benzocyclobutene and biphenylene-based α-amino acid derivatives are prepared in a very high diastereoselective manner *via* a six step sequence using Schöllkopf chiral auxiliary.

Modification of peptides by synthetic (unnatural) amino acids generally increases the stability of the resulting analogs against proteases because they are not recognized as specific substrates. This aspect provides an unique opportunity for synthetic chemist to develop general methodologies[2] that can deliver a range of substitutions which allow the optimization of the side chain at a given position. Furthermore, availability of synthetic α-amino acids (AAA) where only one of the properties such as steric/electronic or hydrophobic varies, while other remain approximately constant makes QSAR studies more meaningful. Studies based on these aspects are rare because of the involvement of more demanding synthetic procedures in utilizing complex amino acids in such type of modifications. In view of varied applications of benzocyclobutene **1** [3] and biphenylene **3** [4] derivatives in organic synthesis, material science and catalysis, we envisioned that an AAA moiety containing these units (e.g., **2**, and **4**) may provide interesting possibilities for post-translational peptide modifications by chemical transformations.



Since a wealth of information is accumulated in the literature regarding the asymmetric derivatization of glycine unit, we choose Schöllkopf chiral auxiliary [5] as a glycine equivalent in the present study. The required bromo derivative **5** was prepared in four step sequence starting from α-chloro-*o*-xylene. Thus, flash vacuum pyrolysis of α-chloro-*o*-xylene (780 ^{o}C/ 0.3mm/Hg) gave benzocyclobutene **1**.[6] Formylation of **1** with $Cl_2CHOMe/TiCl_4$ [7] gave required aldehyde (34% yield) which was reduced to hydroxy derivative by treatment with $NaBH_4$ in methanol at 0 ^{o}C (85% yield). Initial attempts to prepare bromo derivative **5** under PBr_3/ether/pyridine conditions gave the ring opened product along with minor amount of required bromide **5**. After considerable amount of experimentation we found that the required bromide was prepared in 70% isolated yield by treatment of hydroxy derivative with $NaBr/BF_3OEt_2$ in acetonitrile at 0^{o}C. [8] Then, the bromide **5** was treated with mono-anion of Schöllkopf's bis-lactim ether at –78 ^{o}C and the reaction mixture was quenched with water to give **6** in 72% yield after chromatography (**Scheme 1**). The diastereoselectivity of the C-C bond forming alkylation step is very high (>95%). During the purification of **6** we were able to isolate the minor diastereomer in an impure form (≤2%). It is well established that the incoming alkyl group enters *trans* with respect to the isopropyl group during alkylation step. The homogeneity of the major diastereomer formed here is established by ^{13}C NMR[9] data. Hydrolysis of **6** with 1 N HCl gave the amino ester **7** in >90% yield.

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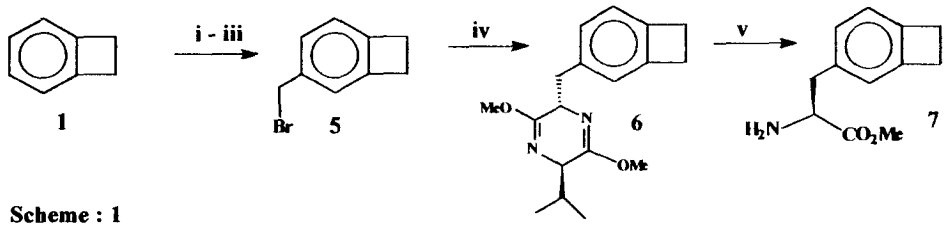


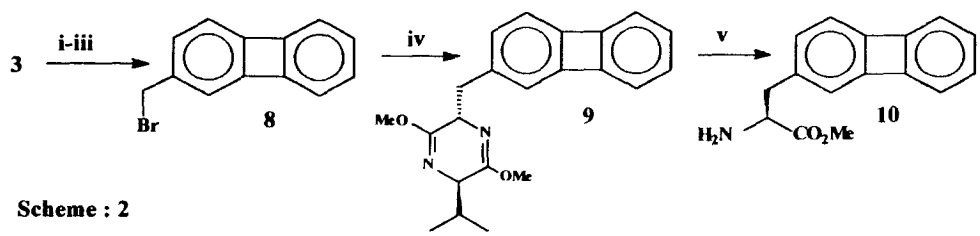
Scheme : 1

i) $TiCl_4$, Cl_2CHOCH_3 ii) $NaBH_4$, MeOH iii) NaBr, BF_3OEt_2, CH_3CN iv) n BuLi, Chiral auxiliary,THF v) 1 N HCl

Next, we turned our attention to the synthesis of biphenylene-based AAA derivatives. Biphenylene **3** is an 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 biphenylene chemistry. Recently, a variety of compounds related to **3** have been prepared and found interesting applications in chemical sciences. For example, Su and co-workers have shown that biphenylene containing monomer unit could be smoothly converted into a highly conjugated polymer under electrochemical oxidation conditions.[9] Biphenylene-based bidentate ligands are known to accelerate Diels-Alder reactions, and also improve the selectivity of Mukaiyama aldol reactions.[10] In addition, biphenylene is anticipated as a unit of new carbon allotropes.[11]

The required biphenylene **3** is prepared by dimerization of benzyne.[12] Thus, diazotization of anthranilic acid gives benzenediazonium-2-carboxylate [13] which was converted into biphenylene **3** in boiling 1,2-dichloroethane. Formylation of biphenylene **3** with dichloromethyl methyl ether in presence of titanium(IV) chloride gave 2-formyl biphenylene in 73% isolated yield after column chromatography.[14] Reduction of formyl derivative with sodium borohydride at 0 °C gave alcohol (m.p.112-113 °C, 87% yield) which on treatment with phosphorus tribromide in benzene gave bromoderivative **8** (m.p. 106-107 °C) in quantitative yield. Reaction of mono-anion of Schöllkopf's bis-lactim ether with bromide **8** at -78°C gave **9** in 74% yield after purification. Hydrolysis of **9** with 1 N HCl gave the hydrolysis product **10** (**Scheme 2**). The other examples studied in this regard are shown in **Table 1**.

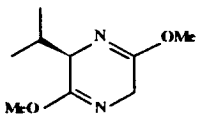
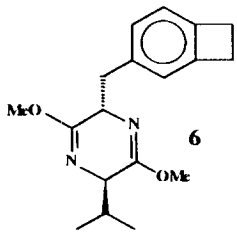
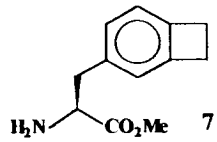
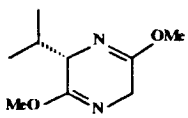
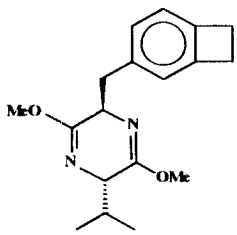
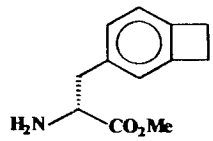
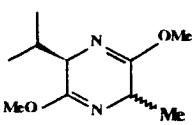
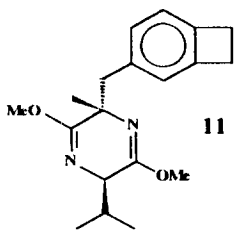
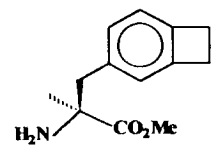
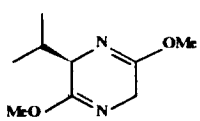
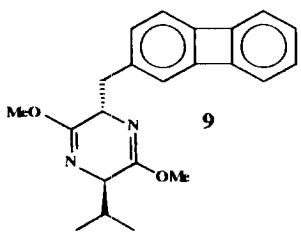
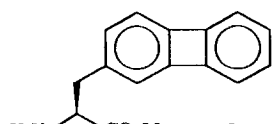
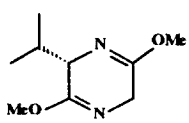
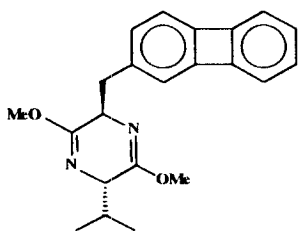
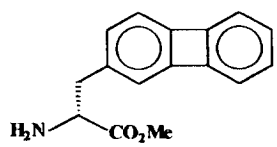
In conclusion, for the first time we have shown the preparation of benzocyclobutene and biphenylene-based AAA derivatives using Schöllkopf chiral auxiliary. We have also demonstrated that $NaBr/BF_3OEt_2$ in acetonitrile protocol is useful for ROH to RBr transformation where cyclobutene ring system is involved. Since unusual AAA derivatives have many applications in organic synthesis and peptide modifications, the AAA derivatives prepared here may find useful applications in bioorganic chemistry and medicinal chemistry. Moreover biphenylene **3** undergoes many interesting transformations under mild reaction conditions, the methodology developed here may find applications in therapeutically useful peptides and peptidomimetics.[15]



Scheme : 2

i) $TiCl_4$, Cl_2CHOMe ii) $NaBH_4$, MeOH iii) PBr_3, C_6H_6 iv) n-BuLi, Chiral auxiliary v) 1 N HCl

Table:1

S.No	Chiral Auxiliary	Coupling Product [a]	Yield(%)	Hydrolysis Product [b]
1		 6	73	 7
2			69	
3		 11	74	
4		 9	74	 10
5			75	

a) de of the coupling product is >95%. b) Yields of the hydrolysis products are in the range of 94 -98%.

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▲^{13}C NMR ($CDCl_3$ at 75.0 MHz) data and specific rotation for selected compounds.

(6)δ 163.8 162.7, 145.2, 143.6, 135.9, 128.6, 124.1, 121.8, 60.3, 56.9, 52.4 52.2, 40.6, 31.3, 29.4, 29.2, 19.1, 16.5; **(7)** δ 175.3, 146.1, 144.3, 135.5, 127.9, 123.4, 122.6, 55.9, 52.0, 41.4, 29.4, 29.3; **(9)** δ 164.0, 162.4, 151.3, 150.8, 149.3, 137.8, 129.3, 128.1, 127.9, 119.6, 117.1, 117.0, 60.4, 56.5, 52.2, 40.5, 31.3, 19.1, 16.6, 16.4; **(10)** δ 175.4, 151.8, 151.0, 149.8, 137.4, 128.7, 128.4, 128.2, 118.6, 117.5, 117.3, 55.6, 52.1, 41.6, 29.7; **(11)** δ 164.3, 161.8, 144.9, 143.5, 136.1, 128.6, 124.2, 121.8, 60.6, 59.9, 52.1, 51.9, 48.0, 30.7, 29.3, 29.2, 28.6, 19.2, 16.7

(6) C=1, $[\alpha]_D$ +20.9 **(7)** C=0.42, $[\alpha]_D$ -9.9 **(9)** C=2, $[\alpha]_D$ + 21.29 **(10)** C=0.8, $[\alpha]_D$ -10.26 **(11)** C=1, $[\alpha]_D$ +18.1

Specific rotations are recorded in absolute ethanol at 25 ^{0}C

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