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DESIGN AND SYNTHESIS OF CONFORMATIONALLY CONSTRAINED BICYCLO[2.2.2]OCTANE-BASED UNUSUAL α-AMINO ACID DERIVATIVES VIA THE DIELS–ALDER REACTION

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Abstract – We report a simple synthetic approach to various conformationally constrained bicyclic *α*-amino acid derivatives using the Diels–Alder reaction as a key step. Moreover, we have investigated the reactivity pattern of various anthracene derivatives in relation to the Diels–Alder chemistry.

INTRODUCTION

Conformationally constrained *α*-amino acids (AAAs) (e.g. **1–3** and **6–7**)[1–5] play a significant role in peptidomimetics. In this regard, various synthetic methods based on Strecker synthesis, Bucherer–Bergs method, and Diels–Alder (DA) strategy have been developed. Sterically constrained AAAs such as *α*-aminoisobutyric acid (Aib) **1** is known to be useful in the peptide design. For example, by incorporation of Aib **1** the resulting peptides adopt *α*-helical and/or *β*-sheet confirmation.[1a] To design peptidomimetics and peptide catalysts, racemic or meso unusual AAAs are also useful because when they are coupled with optical pure proteinogenic AAA two diastereoisomers are formed and these isomers can be separated by conventional techniques.[1b]

To assemble constrained phenylalanine (Phe) derivatives by the DA reaction, methyl 2-acetamidoacrylate (**4)** has been used as a useful synthon. In another occasion, various constrained bicyclic aliphatic AAAs[2b–c] (e.g. **2a**–**b**) are assembled by the DA reaction of dehydroalanine derivatives. The constrained phenylalanine derivatives such as **3a**–**b**[2] were prepared by the Bucherer–Bergs reaction or Strecker synthesis. On the other hand, highly constrained bicyclic AAA derivative (e.g., **6**)[6a] has been synthesized by the DA reaction of methyl 2-acetamidoacrylate (**4**) and anthracene (**5**). It is worth mentioning that, this strategy has found to be useful to design non-steroidal bioactive molecules.[6b–i] Furthermore, this

†This paper is dedicated to Prof. Isao Kuwajima on the occasion of his 77th birthday.

methodology has been extended to 9-substituted anthracene derivatives to generate the substituted bicyclic constrained AAA derivatives **7** involving regioselective DA reaction[7] (Figure 1). Therefore, systematic investigation was launched to design bicyclo[2.2.2]octane related AAA derivatives, that are useful in medicinal chemistry.

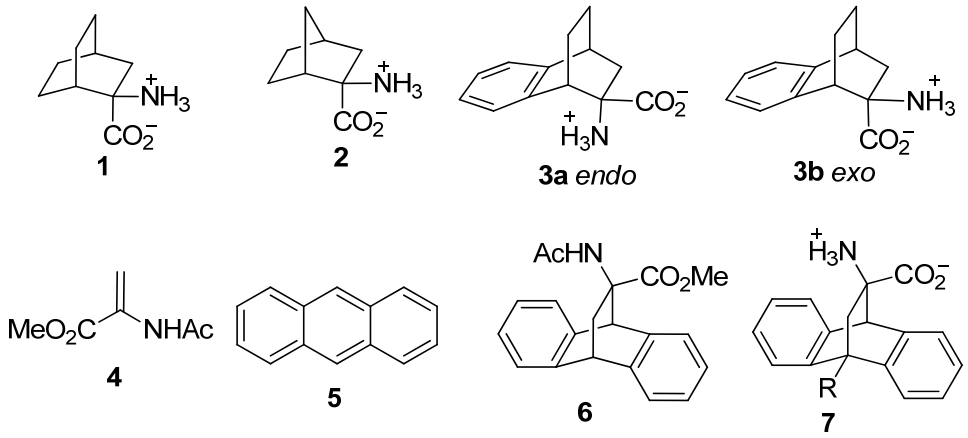


Figure 1. Conformationally constrained bicyclic AAA derivatives and some precursors

In view of our interest to generate various unusual AAA derivatives, we had generated *o*-xylylene (or *o*-quinodimethane) derivatives such as **8** and **9**[8,9] and trapped them with methyl 2-acetamidoacrylate (**4**) in a DA fashion[8–20] to deliver various constrained AAA derivatives. In this context, now we plan to generate a higher analog of **9**, such as **10** and react it with methyl 2-acetamidoacrylate (**4**) to design unusual AAA derivatives (Figure 2).

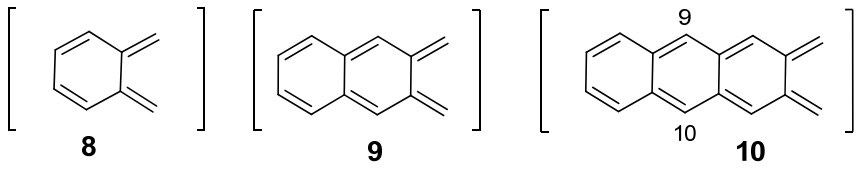


Figure 2. Various *o*-quinodimethane derivatives **8**–**10**

To this end, here we report the reactivity pattern of anthracene derivatives **11**–**13** in connection with the DA chemistry. Various dienophile such as methyl 2-acetamidoacrylate (**4**) and dimethyl acetylenedicarboxylate (DMAD) were reacted with these anthracene derivatives. It is worth mentioning that two possible reactive sites are available in **10** during the DA reaction. The first choice involves the DA reaction of the dienophile at 9,10 position and the other option involves the dienophile reacting at outer portion of the diene. We are also keen to probe the role of the substituents in anthracene derivatives such as **11**–**13** during the DA reaction with methyl 2-acetamidoacrylate (**4**) (Figure 3).

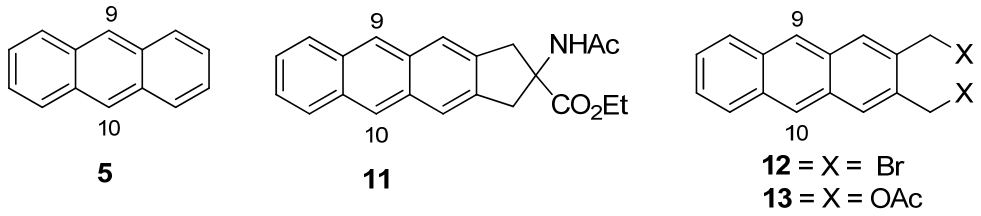


Figure 3. List the anthracene and its derivatives **11**–**13** used in DA chemistry

STRATEGY

Toward the synthesis of various conformationally constrained AAA derivatives,[21–27] we identified the known dibromoanthracene **12** as a key intermediate. Sultine **14**, which can be generated from the dibromide **12** on thermal activation may produce the transient diene **10**. Alternatively, the DA reaction of **12** with dimethyl acetylenedicarboxylate (DMAD) can deliver another key dibromide **15**, which is useful to prepare various constrained AAA derivatives **17**–**18**. Similarly, **11** on DA reaction with DMAD can also generate **19** (Figure 4).

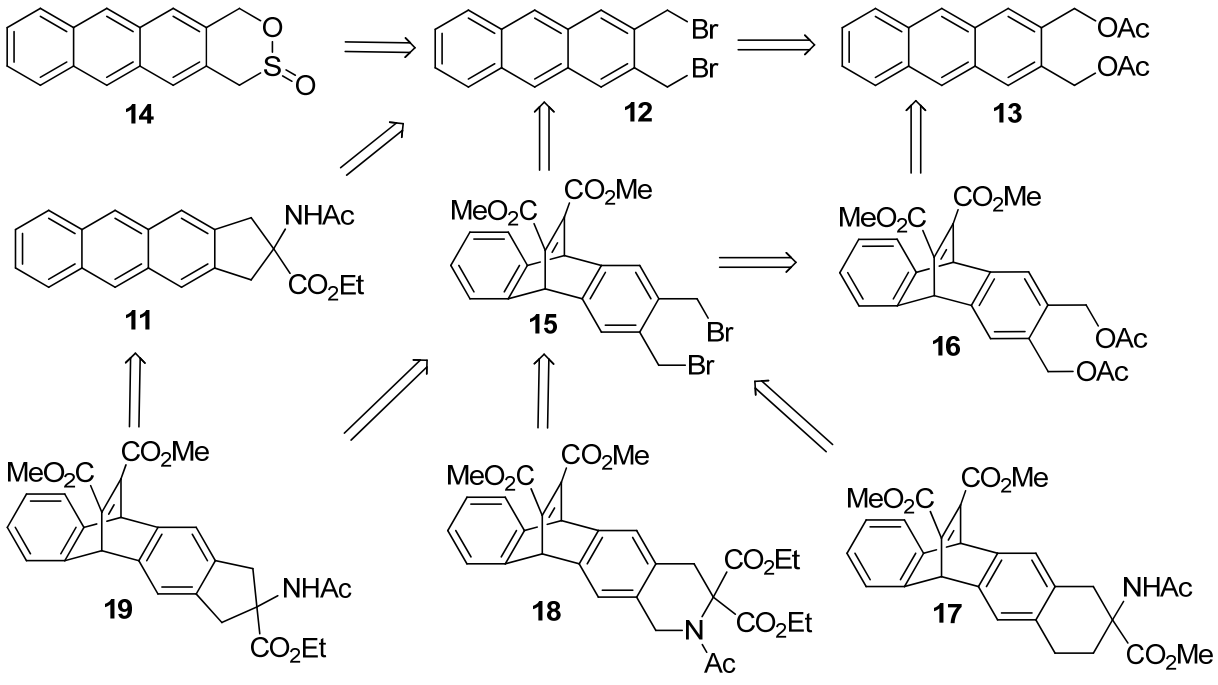


Figure 4. Retrosynthetic pathways to various bicyclic AAA derivatives

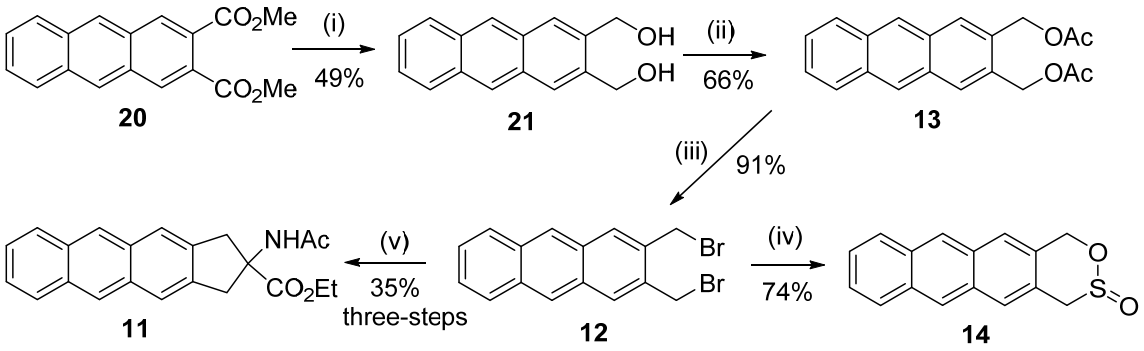
RESULTS AND DISCUSSION

The DA reaction has been identified as a key step to design various bicyclic AAA derivatives **17**–**19**. To

this end, the known 2,3-bis(bromomethyl)anthracene (**12)** was chosen as a key intermediate and it was prepared by following the literature procedure.[28,29]

Initially, the reduction[30–33] of anthracene-2,3-dicarboxylic acid did not give the diol **21**. Later, the dimethyl ester **20** was treated with $LiAlH_4$, in dry THF at low temperature (–12) to 0 ºC for 2 h to afford the desired diol **21**. Formation of the diol was confirmed by the ^1H and ^{13}C NMR spectral data and further supported by mass spectral data. Here, the diol **21** was isolated (49%) first time. Next, the diol was reacted with acetic anhydride in the presence of dry pyridine to furnish a pale-yellow colored 2,3-bis(acetoxymethyl)anthracene (**13**) in 66% yield after crystallization with hot methanol/dichloromethane mixture. Subsequently, the diacetate **13** was subjected to bromination with 33% HBr in glacial acetic acid to afford the yellow colored 2,3-bis(bromomethyl)anthracene (**12**) in 91% yield after crystallization with hot methanol/dichloromethane mixture.

Next, treatment of the dibromide **12** with ethyl isocyanoacetate (EICA) (**23**)[34,35] in the presence of tetrabutylammonium hydrogen sulfate (TBAHS) as phase-transfer catalyst (PTC) and K_2CO_3 as a base gave the crude isonitrile derivative, which was directly subjected to hydrolysis in absolute ethanol and conc. hydrochloric acid, and the subsequent acetylation in the presence of acetic anhydride in dry MeCN at room temperature afforded the anthracene based AAA derivative **11** in 35% yield (three-steps). Alternatively, the dibromide **12** was treated with a readily available sodium hydroxymethane sulfinate (rongalite) **22** under PTC conditions using tetrabutylammonium bromide (TBAB) in DMF to generate the anthracene-based sultine **14** in 74% yield. Since sultine **14** is partially soluble in most of the organic solvents, it was further purified by crystallization with hot CCl_4. The formation of the sultine was confirmed by the ^1H and ^{13}C NMR data and further supported by mass spectral data (Scheme 1).



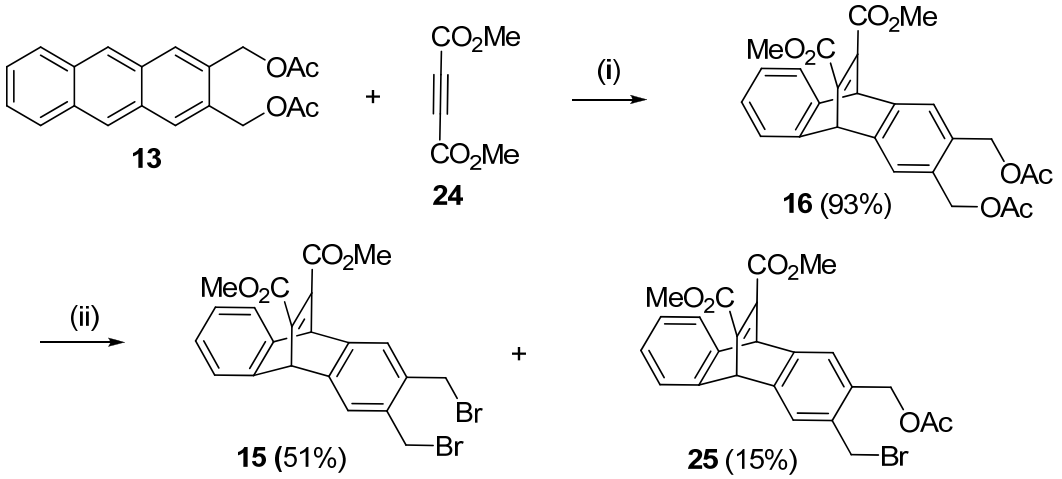
Reagents and conditions: (i) $LiAlH_4$, THF, (–12) – (0 °C), 2 h; (ii) Ac_2O, pyridine, rt, 20 h; (iii) 33% HBr in AcOH, CH_2Cl_2, rt; (iv) rongalite **22**, DMF, TBAB, 0 °C–rt; (v) (a) EICA **23**, TBAHS, K_2CO_3, MeCN, 75 °C, 21 h; (b) CH_2Cl_2, dry EtOH, conc. HCl; (c) MeCN, Ac_2O, rt, 24 h.

Scheme 1. Synthesis of anthracene-based AAA derivative **11** and sultine **14**

Next, the DA reaction of the sultine **14** was attempted with methyl 2-acetamidoacrylate (**4**) in toluene at 75–80 °C for 24 h and subsequently in toluene reflux for 3 days. Surprisingly, the starting material was recovered and the identity of the starting material was confirmed by the ^{1}H NMR spectral data. Later, the sultine **14** was treated with the dienophile **4** in toluene under MWI conditions at 60 W; the desired cycloaddition product was not realized. Further, treatment of the sultine **14** with the same dienophile **4** in *o*-dichlorobenzene under reflux conditions did not afford the desired cycloadduct.

Having the AAA derivative **11** in hand, we have attempted the DA reaction with methyl 2-acetamidoacrylate (**4**) in toluene reflux for 10 days. In spite of several such attempts, the starting material **11** was recovered and it was confirmed by the ^{1}H NMR spectral data. Later, the Lewis acid mediated DA reaction by using BCl_3[36] and Et_2AlCl[37] was also found to be unsuccessful. Then, treatment of the compound **11** with **4** under MWI (70 W), the desired cycloaddition product was not realized. Next, treatment of the compound **11** with another dienophile, such as DMAD (**24**) under toluene reflux condition for 3 days did not afford the expected cycloadduct.

Later, we chose the other anthracene derivatives, such as 2,3-bis(bromomethyl)anthracene (**12**) and 2,3-bis(acetoxymethyl)anthracene (**13**) to realize the cycloaddition reaction. To this end, the compound **12** was reacted with methyl 2-acetamidoacrylate (**4**) in toluene (sealed-tube) at 140 °C for 3 days and under these conditions did not deliver the desired cycloadduct. Similarly, treatment of 2,3-bis(acetoxymethyl)anthracene (**13**) with the compound **4** under the same reaction conditions did not afford the desired product. Surprisingly, the starting material was recovered and its identity was confirmed by the ^{1}H NMR spectral data. Later, we have attempted ionic-liquid[38] conditions to realize the DA reaction of the compound **13** with **4** and in this case also we found no desired cycloadduct formation.

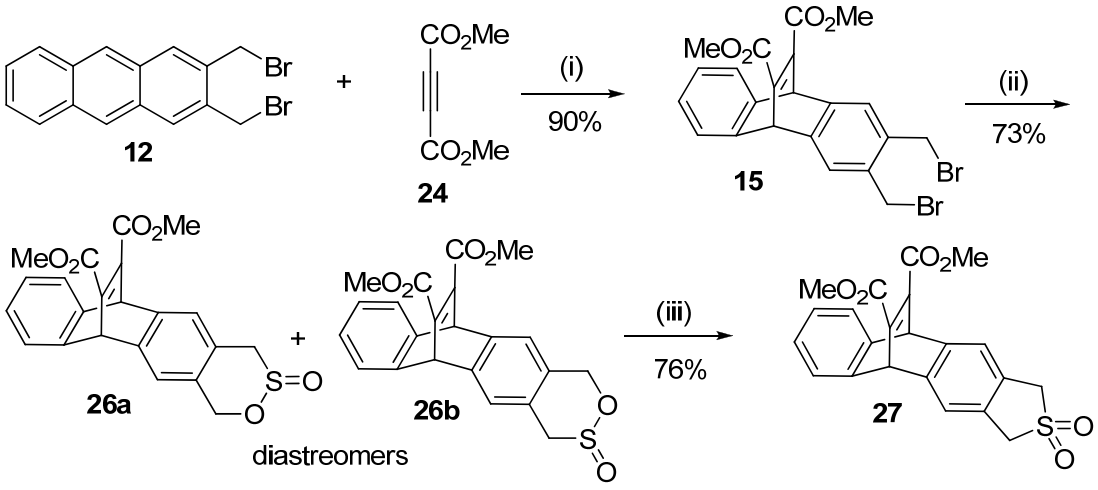


Reagents and conditions: (i) toluene, reflux, 3 days, (ii) 33% HBr in AcOH, CH_2Cl_2, rt, 39 h.

Scheme 2. Synthesis of the bicyclic compound **15** and **25**

Since DMAD (**24**) is a better dienophile[39] for the DA reaction as compared to a methyl 2-acetamidoacrylate (**4**), the 2,3-bis(acetoxymethyl)anthracene (**13**) was reacted with DMAD (**24**) under toluene reflux conditions. As expected the desired cycloadduct **16** was obtained as a viscous liquid in 93% yield, which was purified and then identified by ^{1}H and ^{13}C NMR spectroscopy techniques and further supported by mass spectral data (Scheme 2). Later, treatment of the DA adduct **16** with 33% HBr in acetic acid at room temperature for 39 h gave the corresponding dibromide **15** as a white solid in 51% yield along with the monobrominated product **25** in 15% yield.

Along similar lines, 2,3-bis(bromomethyl)anthracene (**12**) was reacted with DMAD (**24**) in refluxing toluene to furnish the desired cycloadduct **15** in excellent yield 90% (Scheme 3). Next, the cycloadduct **15** was treated with rongalite **22** in the presence of TBAB as a PTC to afford the desired sultine **26** in 73% yield, and NMR data showed the presence of diasteromers. Further, bicyclic sultines **26a** and **26b** were rearranged to sulfone **27** (76% yield) under toluene refluxing conditions.

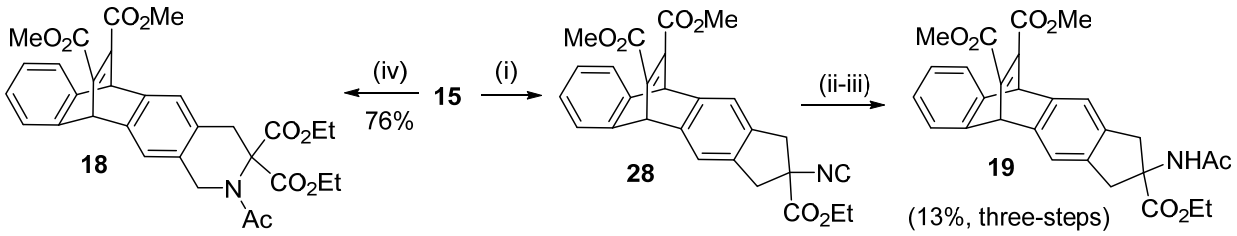


Reagents and conditions: (i) sealed-tube, toluene, 140 °C, 37 h;
(ii) rongalite **22**, TBAB, DMF, 0 °C–rt, 6 h; (iii) toluene, reflux, 24 h.

Scheme 3. Synthesis of sultine **26** and sulfone **27**

Later, the cycloadduct **15** was treated with ethyl isocyanoacetate (**23**) in the presence of K_2CO_3 and PTC in refluxing MeCN conditions gave the coupling product **28**. The coupling product was not purified and it was directly hydrolyzed in conc. hydrochloric acid/absolute ethanol mixture to furnish the desired amino ester. Subsequent acetylation of the amino ester with acetic anhydride in MeCN at room temperature gave the expected acylated product **19** (13%, three-steps, overall yield). TLC indicates a mixture of

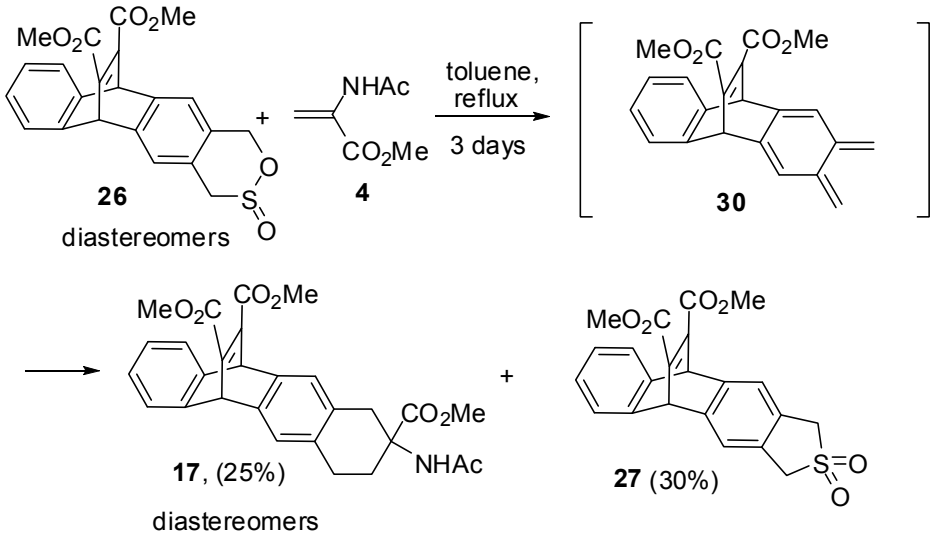
diasteromers of **19**. However, we have isolated a single diastereomer by preparative TLC and identified by spectral data. Alternatively, the compound **15** was reacted with diethyl acetamidomalonate (DEAM) **29** in the presence of K_2CO_3 as a base in MeCN refluxing condition to furnish the desired Tic derivative **18** in 76% yield (Scheme 4).



Reagents and conditions: (i) EICA **23**, TBAHS, K_2CO_3, MeCN, 75 °C, 21 h; (ii) CH_2Cl_2, dry EtOH, conc. HCl; (iii) MeCN, Ac_2O, rt, 24 h; (iv) DEAM **29**, K_2CO_3, MeCN, reflux, 15 h.

Scheme 4. Synthesis of Tic-based **18** and indan-based **19** AAA derivatives

Having the sultine **26** in the hand, we attempted the synthesis of the tetralin-based AAA derivative **17** via the cycloaddition reaction. To this end, the bicyclic sultine **26** was reacted with methyl 2-acetamidoacrylate (**4**) in refluxing toluene for 3 days to furnish the tetralin-based AAA derivative **17** in 25% yield as a mixture of diastereomers. Here, the rearranged sulfone **27** was also isolated in 30% yield (Scheme 5).



Scheme 5. Synthesis of tetralin-based AAA derivative **17**

It is interesting to note that the sultine derivative **14** containing anthracene ring did not undergo DA reaction with methyl 2-acetamidoacrylate (**4**). However, the conjugation present in **14** is destroyed by formation of the DA adduct **26**, and therefore **26** undergo DA reaction with **4**.

Herein, we have successfully synthesized conformationally constrained bicyclic AAA derivatives such as tetralin-based AAA derivative **17** (11 steps), 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) based AAA derivative **18** (10 steps), and indan-based AAA derivative **19** (12 steps) using the DA reaction as a key step. The tetracyclic compound **11**, which contains an additional five membered ring on anthracene system does not behave like anthracene in the DA sequence. The sultine **14** containing anthracene unit does not participate in the DA reaction with methyl 2-acetamidoacrylate (**4**) and dimethyl acetylenedicarboxylate (**24**) even under forcing reaction conditions. However, the compound **26** undergo the DA reaction with **4**.

EXPERIMENTAL

Melting points were recorded on Labhosp or Veego melting point apparatus and are uncorrected. Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra were generally recorded on Varian VXR (400 MHz) or Bruker (400 MHz), spectrometers. Carbon Nuclear Magnetic Resonance (^{13}C NMR) spectra were recorded on Varian VXR (75 MHz) or Bruker (100 MHz) spectrometer. NMR samples were generally made in chloroform-d solvent and chemical shifts were reported in δ scale using tetramethylsilane (TMS) as the internal standard. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder).

All the reactions were monitored by employing TLC technique using appropriate solvent system for development. Transfer of moisture sensitive materials were carried out by using standard syringe-septum techniques and the reactions were maintained under nitrogen atmosphere until the work up. Dry CCl_4 and CH_2Cl_2, were obtained by distillation over P_2O_5. Magnesium sulfate/sodium sulfate was dried in an oven at 130 °C for one day. All the solvent extracts were washed successively with water, brine (saturated sodium chloride solution) and dried over anhydrous magnesium sulfate/ sodium sulfate and concentrated at reduced pressure on a Buchi R-114 rotary evaporator. Yields reported are isolated yields of the products. Ethyl isocyanoacetate was prepared by following the literature procedure[34,35] and methyl 2-acetamidoacrylate and diethyl acetamidomalanate were purchased from Aldrich Chemical Co., inc. Yields refer to the chromatographically isolated yield. All the commercial grade reagents were used without further purification.

Reduction with lithium aluminum hydride ($LiAlH_4$)[28,29]

To a suspension of $LiAlH_4$ (764 mg, 20.10 mmol) in THF (30 mL) at 0 ºC was added the diester **20** (1.18 g, 4.02 mmol) under N_2 with stirring. Then, the reaction mixture was kept at –12 ºC to 0 ºC for 3 h. Later,

the reaction mixture was quenched at 0 ºC by adding saturated solution of Na_2SO_4 (3 mL) in a dropwise manner, stirred for 15 min, the mixture was filtered on a glass wool and the filtrate was evaporated at reduced pressure at 40–50 ºC to obtain the product **21** (469 mg, 49%) as a yellow colored solid.

mp 247–249 ºC; IR (Neat) 3428, 3054, 2987, 1604, 1421, 1265, 740 cm^{-1}; ^1H NMR (400 MHz, CD_3SOCD_3) δ 8.50 (s, 2H, ArH), 8.06-8.04 (m, 2H, ArH), 8.02 (s, 2H, ArH), 7.48-7.46 (m, 2H, ArH), 5.36 (bs, 2H, OH), 4.73 (s, 4H, OCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.2, 131.2, 130.6, 128.0, 125.4, 125.2, 124.7, 60 8; HRMS (Q-ToF MS ES$^+$): *m/z:* $(M+H)^+$ Calcd for $C_{16}H_{15}O_2$: 239.1077. Found: 239.1072.

Synthesis of anthracene sultine (14)

This experiment was conducted by following the earlier procedure.[25]

In a two neck round bottom flask was added rongalite **22** (383 mg, 2.4 mmol) in DMF (6 mL). Later, to an obtained suspension was added dibromo compound **12** (90 mg, 0.24 mmol) and TBAB (37 mg, 0.1 mmol) at 0 ºC and the resulting reaction mixture was stirred (at 0 ºC for 3 h) and then at room temperature for 3 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc. The organic layer was washed with H_2O (2 × 10 mL), brine (2 × 10 mL), dried over anhydrous Na_2SO_4. Evaporation of the organic layer under reduced pressure afforded the crude product. Later, the compound was purified by crystallization using hot CCl_4 to give a yellow colored solid **14** (49.2 mg, 74%).

R_f = 0.36 (silica gel, 10% EtOAc-petroleum ether); mp 250–252 ºC; IR (Neat) 3049, 2923, 1657, 1325, 1264, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H, ArH), δ 8.41 (s, 1H, ArH), δ 8.03-8.00 (m, 2H, ArH), δ 7.92 (s, 1H, ArH), δ 7.91 (s, 1H ArH), δ 7.52-7.48 (m, 2H, ArH), δ 5.58 (½ AB*q*, 1H, *J* = 13.1 Hz), δ 5.17 (½ AB*q*, 1H, *J* = 13.1 Hz), δ 4.74 (½ AB*q*, 1H, *J* = 15.3 Hz), δ 3.83 (½ AB*q*, 1H, *J* = 15.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 132.2, 131.4, 131.2, 129.0, 128.3, 126.6, 126.4, 126.1, 125.5, 124.5, 64.5, 59.1; HRMS (Q-ToF MS ES$^+$): *m/z:* $(M+H)^+$ Calcd for $C_{16}H_{13}O_2S$: 269.0638. Found: 269.0636.

Synthesis of AAA derivative (11)

This experiment was conducted by following the earlier procedure.[29]

In a two neck round bottom flask were added the dibromide **12** (150 mg, 0.41 mmol), tetrabutylammonium hydrogen sulfate (55.5 mg, 0.16 mmol) and K_2CO_3 (1.13 g, 8.19 mmol) in MeCN (15 mL). Later, the resulting reaction mixture was treated with ethyl isocyanoacetate (**23**) (0.5 mL, 4.11 mmol). Then the reaction mixture was stirred at 75–80 °C under N_2 for 22.5 h, then cooled to room temperature, and filtered through a sintered glass funnel. The solid was washed with CH_2Cl_2 and the filtrate was evaporated at reduce pressure to give the crude product, which was directly subjected to hydrolysis without further purification. The crude product in CH_2Cl_2 (12 mL), was reacted with dry EtOH (25 mL) in the presence of conc. HCl (1 mL). The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2 (50 mL), H_2O (75 mL), followed by the addition of $NaHCO_3$ to make it alkaline. Later, the CH_2Cl_2 layer was

washed with H_2O (2 × 30 mL), dried (Na_2SO_4), filtered, and evaporated at reduced pressure gave the crude product was directly subjected to acetylation.

The crude product in dry MeCN (12 mL) was treated with Ac_2O (0.51 mL, 5.44 mmol) at room temperature for 24 h. Evaporation of the solvent under reduced pressure to give the crude product and it was further purified by column chromatography (50% EtOAc/petroleum ether mixture) to give the pure product **11** (49.8 mg, 35%-three-steps) as a white solid.

R_f = 0.49 (silica gel, 50% EtOAc-petroleum ether); IR (Neat) 3054, 2926, 1712, 1605, 1422, 1156, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H, ArH), 7.97-7.95 (m, 2H, ArH), 7.78 (s, 2H, ArH), 7.45-7.42 (m, 2H, ArH), 6.05 (s, 1H, NH), 4.27 (q, 2H, *J* = 7.0 Hz, OCH_2CH_3), 3.78 and 3.47 (d, 2H, *J* = 16.5 Hz, $ArCH_2$ and d, 2H, *J* = 16.5 Hz, $ArCH_2$), 1.92, (s, 3H, $COCH_3$), 1.27 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C=O amide), 170.3 (C=O ester), 139.0, 131.6, 128.1, 125.7, 125.3, 122.8, 66.4, 61.8, 42.7, 23.2, 14.2; HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{22}H_{22}NO_3$: 348.1600. Found: 348.1590.

The DA reaction of diacetate (13) with DMAD (24)

In a 50 mL round bottom flask was added 2,3-bis(acetoxymethyl)anthracene (**13**) (30 mg, 0.09 mmol) was reacted with dimethyl acetylenedicarboxylate (DMAD) (**24**) (1.5 equiv) in toluene (3 mL). The reaction mixture was refluxed for 3 days (TLC monitoring). Evaporation of the solvent gave the crude product, which was further purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether mixture gave the desired product **16** (40.2 mg, 93%) as a viscous semi solid.

R_f = 0.37 (silica gel, 30% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H, ArH), 7.39-7.37 (m, 2H, ArH), 7.04-7.02 (m, 2H, ArH), 5.49 (s, 2H, ArCH), 5.10 (s, 4H, OCH_2), 3.79 (s, 6H, OCH_3), 2.06 (s, 6H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.8 (C=O ester). 146.9, 144.6, 143.3, 131.9, 125.7, 125.6, 124.1, 63.5, 52.6, 52.1, 21.0; HRMS (Q-ToF MS ES^+): *m/z:* $(M+Na)^+$ Calcd for $C_{26}H_{24}O_8Na$: 487.1369. Found: 487.1363.

Conversion of diacetate (16) to the dibromide (15)

To a solution of the diacetate **16** (39 mg, 0.08 mmol) in CH_2Cl_2 (10 mL) was added a 33% HBr in acetic acid (0.5 mL). The solution was stirred at room temperature for 39 h (TLC monitoring). The reaction mixture was quenched with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 10). The organic layer was washed with H_2O (15 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent at reduced pressure gave the crude product, which was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether mixture afforded the desired product **15** (21 mg, 51%) as a white solid along with the mono-brominated product **25** (6 mg, 15%).

Compound **15**

R_f = 0.70 (silica gel, 30% EtOAc-petroleum ether); mp 180–182 °C; IR (Neat) 3054, 2999, 2951, 1717,

1464, 1435, 1267, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H, ArH), 7.37 (s, 2H, ArH), 7.04-7.02 (m, 2H, ArH), 5.46 (s, 2H, ArCH), 4.56 (s, 4H, 2 × CH_2Br), 3.78 (s, 6H, 2 × OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C=O ester), 146.7, 145.1, 143.0, 133.9, 126.4, 125.9, 124.1, 52.6, 52.0, 30.0. HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{22}H_{19}Br_2O_4$: 504.9650. Found: 504.9650.

Compound **25**

R_f = 0.58 (silica gel, 30% EtOAc-petroleum ether); mp 160–162 °C; IR (Neat) 3056, 2953, 1735, 1637, 1436, 1223, 1229, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.39-7.35 (m, 2H, ArH), 7.05-7.01 (m, 2H, ArH), 5.48 (s, 1H, ArCH), 5.47 (s, 1H, ArCH), 5.16 (s, 2H, OCH_2), 4.50 (s, 2H, CH_2Br), 3.78 (s, 6H, 2 × OCH_3), 2.07 (s, 3H $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (OAc), 165.8 (C=O ester), 146.8, 146.8, 144.9, 144.8, 143.2, 133.8, 132.0, 126.1, 126.0, 125.8, 124.1, 63.2, 52.6, 52.1, 52.1, 30.5, 21.1; HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{24}H_{22}BrO_6$: 485.0598. Found: 485.0600.

Synthesis of dibromide (15) via the DA reaction

In a sealed-tube were added 2,3-bis(bromomethyl)anthracene (**12**) (280 mg, 0.76 mmol) in dry toluene (3 mL) along with DMAD **24** (2.5 equiv). The reaction mixture was heated for 37 h (TLC monitoring). Evaporation of the solvent gave the crude product, which was further purified by column chromatography. Elution with 30% EtOAc/petroleum ether mixture afforded the desired product **15** as a white solid (350.7 mg, 90%). The compound formed showed identical ^1H NMR data as obtained in earlier experiment.

Synthesis of bicyclic sultine (26)

To a suspension of rongalite **22** (152 mg, 0.98 mmol) in DMF (6 mL) was added dibromo compound **15** (50 mg, 0.24 mmol) and TBAB (31 mg, 0.096 mmol) at 0 ºC and the resulting suspension was stirred at 0 ºC for 3 h and at room temperature for additional 3 h. The reaction mixture was diluted with H_2O (10 mL) (TLC monitoring) and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O (2 × 10 mL), dried over anhydrous Na_2SO_4. Evaporation of the organic layer under reduced pressure gave the crude product, which was purified by column chromatography. Elution of the column with 50% EtOAc/petroleum ether mixture afforded the product **26** (mixture of isomers) (31 mg, 76%) as a white semi solid.

R_f = 0.33 (silica gel, 30% EtOAc-petroleum ether); IR (Neat) 3056, 2986, 1718, 1436, 1218, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *Isomers*: δ 7.39-736 (m, 2H, ArH), 7.28 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.06-7.02 (m, 2H, ArH), 5.48 (s, 1H, ArCH), 5.48 (s, 1H, ArCH), 5.21 (dd, 1H, J_1 = 12.1, J_2 = 12.5 Hz), 4.89 (dd, 1H, J_1 = 9.2, J_2 = 9.1 Hz), 4.33 (dd, 1H, J_1 = 8.9, J_2 = 8.8 Hz), 3.78 (s, 6H, 2 × OCH_3), 3.46 (dd, 1H, J_1 = 2.8, J_2 = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *Isomers*: δ 165.8, 165.8, 165.7, 165.7 (C=O ester), 146.9, 146.8, 144.6, 144.5, 143.9, 143.9, 143.3, 143.2, 143.1, 143.1, 131.3, 131.0, 125.9, 125.9, 125.3, 125.2, 124.1, 124.0, 123.6, 123.2, 121.5, 121.4, 63.2, 63.2, 57.2, 56.8, 52.6, 52.1; HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$

Calcd for $C_{22}H_{19}O_6S$: 411.0896. Found: 411.0902.

Synthesis of bicyclic sulphone (27)

In a 50 mL round bottom flask was added sultine **26** (20 mg) in toluene (3 mL) and then the reaction mixture was refluxed for 24 h (TLC monitoring). Evaporation of the solvent gave the crude product, which was further purified by column chromatography. Elution of the column with 40% EtOAc/petroleum ether mixture afforded the desired product **27** (15 mg, 73%) as a white semisolid.

R_f = 0.71 (silica gel, 40% EtOAc-petroleum ether-double run); IR (thin film) 3055, 2986, 2953, 1719, 1437, 1320, 1216, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H, ArH), 7.32 (s, 2H, ArH), 7.06-7.04 (m, 2H, ArH), 5.48 (s, 2H, ArCH), 4.29 (d, J = 15.7 Hz, 2H), 4.23 (d, J = 15.6 Hz, 2H) 3.79 (s, 6H, 2 × OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C=O ester). 146.6, 145.1, 142.9, 128.3, 126.0, 124.1, 121.7, 56.9, 52.7, 52.2; HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{22}H_{19}O_6S$: 411.0892. Found: 411.0902.

Synthesis of indan-based AAA derivative (19)

To a suspension of the dibromide **15** (100 mg, 0.19 mmol), tetrabutylammonium hydrogen sulfate (32 mg, 0.095 mmol) and K_2CO_3 (262 mg, 1.9 mmol) in MeCN (15 mL) was added ethyl isocyanoacetate (**23**) (10 equiv). The reaction mixture was stirred under N_2 at 75–80 °C for 15 h, then cooled to room temperature, and filtered through sintered glass funnel. The solid was washed with CH_2Cl_2 and the filtrate was evaporated *in vacuo* to afford the desired isonitrile product **28**. The crude product obtained was directly subjected to hydrolysis without further purification.

The crude isonitrile derivative **28** was hydrolysed in absolute EtOH (15 mL) in the presence of conc. HCl (1 mL). The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2 (50 mL), H_2O (75 mL), and the mixture was made alkaline by slow addition of $NaHCO_3$ with stirring. The separated CH_2Cl_2 layer was washed with H_2O (2 × 25 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude amino product. The product obtained, which was directly subjected to acetylation. The crude product in dry MeCN (15 mL) was reacted with Ac_2O (1.5 mL,) at room temperature for 24 h. Evaporation of the solvent gave the crude product, which was purified by column chromatography. Elution of the column with 50% EtOAc/petroleum ether mixture gave pure product **19** (12 mg, 13%, three-steps) as a pale yellow semi solid.

R_f = 0.31 (silica gel, 50% EtOAc-petroleum ether); IR (Neat) 3055, 2985, 2929, 1731, 1682, 1437, 1218, 1061, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H, ArH), 7.21 (s, 2H, ArH), 7.04-6.99 (m, 2H, ArH), 5.97 (s, 1H, NH), 5.42 (s, 2H, ArCH), 4.21 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 3.78 (s, 6H, 2 × OCH_3), 3.55 and 3.10 (d, 2H, J = 16.5 Hz, $ArCH_2$, and d, 2H, J = 16.6 Hz, $ArCH_2$), 1.83 (s, 3H, $COCH_3$), 1.25 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C=O amide), 170.2, 166.0, (C=O ester), 147.2, 144.0, 143.5, 137.0, 125.6, 123.9, 120.5, 66.3, 61.8, 52.6, 52.5, 43.3, 29.8, 23.3, 14.2; HRMS (Q-ToF

MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{28}H_{28}NO_7$: 490.1854. Found: 490.1866.

Synthesis of Tic-based AAA derivative (18)

To a suspension of the dibromide **15** (60 mg, 0.12 mmol) and K_2CO_3 (82 mg, 0.59 mmol) in MeCN (15 mL) was added diethyl acetamidomalonate (DEAM) **29** (26 mg, 0.12). The reaction mixture was stirred under N_2 at 75–80 °C for 15 h, then cooled to room temperature, and filtered through sintered glass. The solid was washed with CH_2Cl_2 and the filtrate was evaporated under reduced pressure. The crude product obtained was purified by column chromatography. Elution of the column with 50% EtOAc/petroleum ether mixture gave the pure product **18** (51 mg, 76%) as a white semi solid.

R_f = 0.46 (silica gel, 40% EtOAc-petroleum ether); IR (Neat) 3058, 2984, 2954, 1732, 1682, 1436, 1394, 1232, 1060, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H, ArH), 7.18 (s, 2H, ArH), 7.04-7.00 (m, 2H, ArH), 5.43 (s, 1H, ArCH), 5.42 (s, 1H, ArCH), 4.61 (d, 2H, *J* = 4.6 Hz, $ArCH_2$), 4.15 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.04 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.36 (d, 2H, *J* = 4.9 Hz, $ArCH_2$), 2.24 (s, 3H, $COCH_3$), 1.12 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 0.94 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C=O amide), 167.9, 165.9, 165.8 (C=O ester), 147.1, 146.6, 143.7, 143.4, 129.8, 129.6, 125.7, 123.9, 123.5, 121,9, 68.0, 62.1, 62.0, 52.6, 52.2, 52.1, 47.9, 37.3, 22.5, 13.9, 13.7; HRMS (Q-ToF MS ES^+): *m/z:* $(M+H)^+$ Calcd for $C_{31}H_{32}NO_9$: 562.2087. Found: 562.2077.

Synthesis of tetralin-based AAA derivative (17)

To a solution of bicyclic sultine **26** (29 mg, 0.07 mmol) in toluene (3 mL) was added methyl 2-acetamidoacrylate (**4**) (15 mg, 0.07 mmol). The resulting reaction mixture was refluxed for 3 days (TLC monitoring). Evaporation of the solvent gave the crude mixture, which was further purified by column chromatography. Elution of the column with 50% EtOAc/petroleum ether mixture afforded the corresponding sulphone **26** (8.7 mg, 30% yield) and further elution with 70% mixture of EtOAc and petroleum ether afforded the desired product **17** (semi solid, 8.4 mg, 25%) as mixture of isomers.

R_f = 0.28 (silica gel, 40% EtOAc-petroleum ether); IR (Neat) 3273, 3054, 2986, 2953, 1735, 1684, 1437, 1220, 1060, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *Isomers*: δ 7.39-7.35 (m, 2 × 2H, ArH), 7.14 (s, 2 × 1H, ArH), 7.07 (s, 2 × 1H, ArH), 7.05-7.01 (m, 2 × 2H, ArH), 5.63, 5.52 (s, 2 × 1H, 2NH), 5.41, 5.40, (s, 2 × 2H, bridge head, 2 × CH), 3.79, 3.79 (s, 2 × 3H, 2 × OCH_3), 3.78, 3.78 (s, 2 × 3H, 2 × OCH_3), 3.75, 3.74 (s, 2 × 3H, 2 × OCH_3), 3.17 (t, 2 × 1H, *J* = 16.9 Hz, CH_2), 2.88-2.81 (m, 2 × 1H, CH_2), 2.79-2.60 (m, 2 × 2H, CH_2), 2.58-2.51 (m, 2 × 1H, CH_2), 2.05-2.01 (m, 2 × 1H, CH_2), 1.95, 1.85 (s, 2 × 3H, 2 × $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *Isomers*: δ 174.0 (NHCO), 170.3, 170.2 (2 × CO_2Me), 166.2, 166.1, 166.0, 166.0, 147.2, 147.0, 146.9, 143.9, 143.6, 143.6, 142.4, 142.3, 141.9, 141.8, 132.1, 132.1, 128.7, 125.7, 125.7, 125.0, 124.5, 124.5, 123.9, 57.8, 57.8, 52.8, 52.7, 52.6, 52.6, 52.0, 52.0, 38.1, 38.1, 27.6, 27.6, 25.2, 23.2, 23.2;

HRMS (Q-ToF MS ES$^+$): *m/z:* $(M+H)^+$ Calcd for $C_{28}H_{28}NO_7$: 490.1869. Found: 490.1866.

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