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Novel α-substituted β-amino diesters from acylnitroso-derived hetero-Diels–Alder cycloadducts

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Abstract—α-Methyl β-amino diesters were synthesized in a simple three-step procedure starting from acylnitroso-derived Diels–Alder adducts of cyclopentadiene. Treatment of the cycloadducts with copper catalyst-modified methylmagnesium bromide gave *anti*-1,2-cyclopentenyl hydroxamic acids. Reduction of the hydroxamate N–O bond with titanium(III) chloride followed by ozonolytic cleavage of the cyclopentenyl olefin provided the desired α-methyl β-amino diesters.

1. Introduction

β-Amino diacids (**1**, $R_1=R_2=H$) and diesters (**1**, R_1, R_2=alkyl) have served as valuable intermediates in the synthesis of a variety of biologically interesting molecules (Fig. 1). For example, analogs of the C-terminal tetrapeptide of gastrin (**2**) were synthesized from β-homo aspartic acid (**1**, $R_1=t$-Bu, $R_2=H$, $R_3=H$, R_4=Cbz) and showed potent gastrin antagonist activity.[1] Harada and co-workers synthesized interesting polypeptides **3** from 3-aminoglutaric acid (**1**, $R_1=R_2=R_3=R_4=H$).[2,3] Both enantiomers of 3,4-diaminobutyric acid **4** were constructed from β-amino diester **1** ($R_1=t$-Bu, R_2=Me, $R_3=H$, R_4=Cbz) and served as synthons for heterocyclic GABA-receptor agonists.[4] Hultin and Jones showed that β-amino diesters **5** were allosteric activators of trypsin catalysis.[5] Amide-linked triacridines **6** were synthesized as potential antitumor agents from Boc-3-aminoglutaric acid (**1**, $R_1=R_2=R_3=H$, R_4=Boc).[6] Diethyl β-pyrrolidinylgluconate [**1**, $R_1=R_2$=Et, R_3, $R_4=CH_2(CH_2)_2CH_2$] was used to construct phenol **7**, a potential intermediate in the synthesis of natural products containing linear aromatic systems.[7] Substituted-9-azabicyclo[3.3.1]nonan-3-ones, such as 3,7-dione derivative **8**, often possess a wide spectrum of biological activities, including anticholinergic, antidepressant, neuroleptic, cardiovascular, antiparkinsonian, antidiabetic, and antitussive activities. Compound **8** was synthesized from β-amino diester **1** ($R_1=R_2$=Et, $R_3=R_4=H$).[8] While β-amino diacids and diesters have enjoyed a broad range of synthetic applications as demonstrated above, they have been used most extensively as precursors to β-lactams **9**.[9] Herein, we report a novel synthetic strategy for the construction of β-amino diesters.

Carbapenems **9** makes up an important class of β-lactam antibiotics with a wide spectrum of action against Gram-positive and Gram-negative bacteria. They also have potent in vitro and in vivo activity against the clinically important *Pseudomonas aeruginosa*.[10] The potent activity of carbapenems has been attributed to good diffusion through the bacterial outer membrane, high affinity for penicillin-binding proteins, and high stability and inhibitory activity against β-lactamases. Extensive SAR studies have shown that 1β-methyl carbapenems (**9**, $R_5=CH_3$) are among the most potent in this class of antibiotics.[11]

Even after decades of research, carbapenems continue to capture the attention of synthetic chemists.[9] The densely functionalized bicyclic core of carbapenems offers a number of synthetic challenges, including the ability to obtain the required β-stereochemistry at the C(1) position. Opening the synthetically versatile acylnitroso Diels–Alder cycloadduct **10** with various Grignard reagents was envisioned to provide *anti*-1,2-cyclopentenes **11** that could be converted into α-substituted β-amino diesters **12**. These diesters (**12**) possess the required relative stereochemistry to serve as precursors to 1β-substituted carbapenems **13** (Scheme 1).

Keywords: acylnitroso; β-amino diesters; 1β-methyl carbapenems; Grignard; hydroxamic acid.

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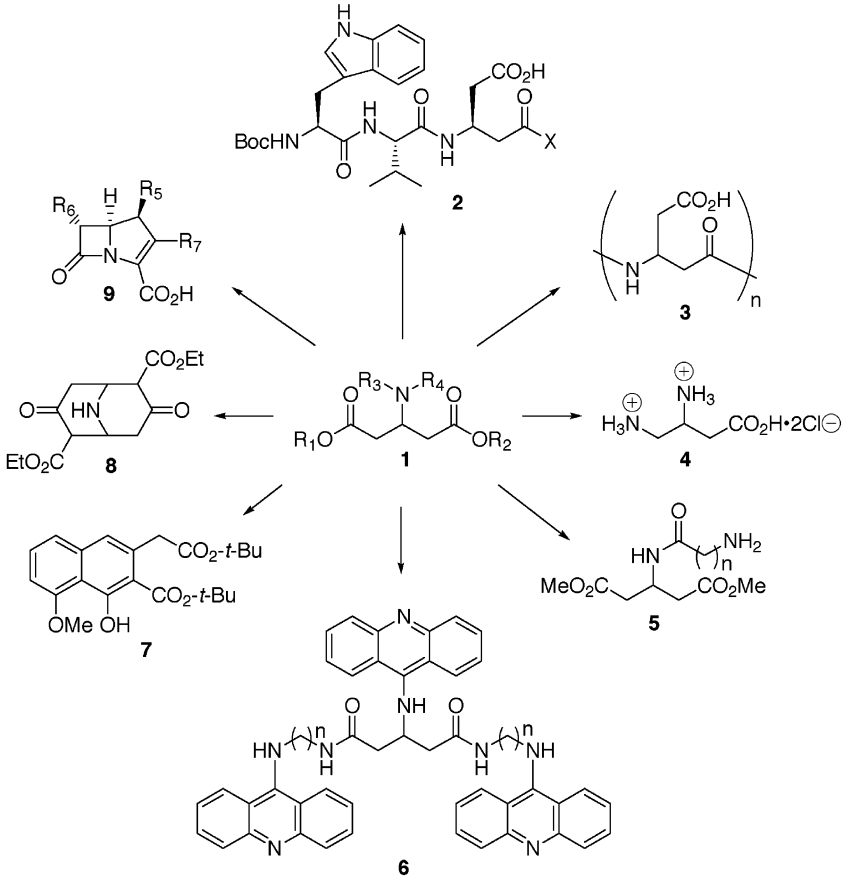
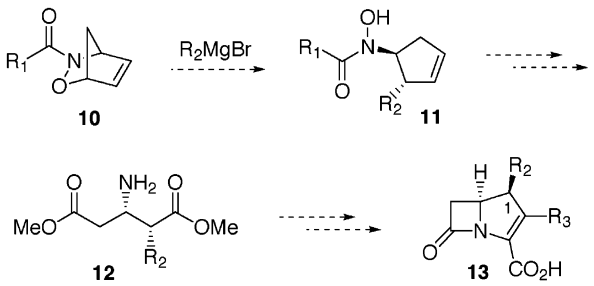


Figure 1.

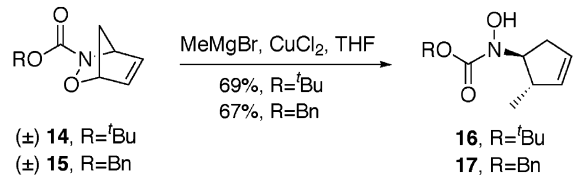


Scheme 1.

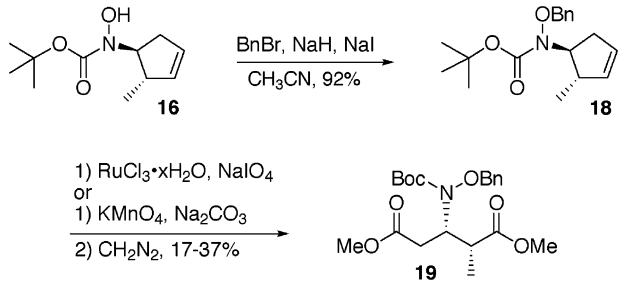
2. Results and discussion

The synthesis of α-substituted β-amino diester **12** (R_1 = Me) began with the opening of *N*-Boc cycloadduct **14** and *N*-Cbz cycloadduct **15** with methylmagnesium bromide (Scheme 2).[12] An initial attempt at the ring opening of cycloadduct **14** in the absence of any copper catalyst gave an unexpectedly low yield (12%) of a 1.6:1.4:1 ratio of *anti*-1,2-(**16**):*anti*-1,4-:*syn*-1,4-products. Inclusion of a catalytic amount of copper(II) increased both the yield and selectivity of the reaction. Use of ten mole percent of copper(II) chloride gave a 90% yield of a 27:8:1 ratio of *anti*-1,2-(**16**):*anti*-1,4-:*syn*-1,4-products.[14,16a] This corresponded to an approximately 70% yield of the desired and separable *anti*-1,2-product **16**. Similarly, treatment of *N*-Cbz cycloadduct **15** with methylmagnesium bromide in the presence of a catalytic amount of copper(II) chloride provided a 98% yield of a 2.2:1 mixture of *anti*-1,2-(**17**):*anti*-1,4-products, corresponding to a 67% yield of the desired and separable product **17**.[16b,17] Attempts to further optimize the reaction by changing the solvent from tetrahydrofuran to diethyl ether were unsuccessful. When copper was used in ether, the reaction with cycloadduct **14** gave a 71% yield of a 13.5:4:1 ratio of *anti*-1,2-(**16**):*anti*-1,4-:*syn*-1,4-products, and when copper was omitted, only a 27% yield was obtained.

The synthesis was first continued with the benzyl protection of *N*-Boc hydroxamic acid **16**, which proceeded smoothly in 92% yield (Scheme 3). The next step involved the oxidative cleavage of the cyclopentenyl olefin. Initial attempts using ruthenium tetraoxide followed by treatment with diazomethane gave rather low



Scheme 2.



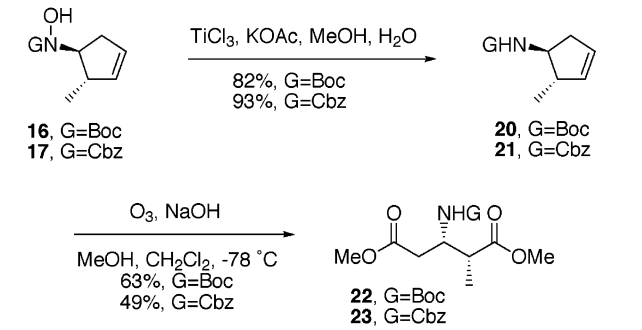
Scheme 3.

yields (up to 37%). An attempt was made to use potassium permanganate as the oxidant, however the yield was still quite low (17%).

The possibility of hydroxamate **18** binding to the metal oxidants was thought to contribute to the inefficiency of these oxidative cleavage reactions. In order to alleviate this potential problem, a somewhat different approach to the β-amino diester synthesis was taken. The modified synthesis involved reducing the hydroxamic acid N–O bond prior to the oxidative cleavage of the olefin. Hydroxamic acids **16** and **17** were treated with titanium(III) chloride in a pH 7 potassium acetate buffer to give amines **20** and **21** in good yields (82 and 93%, respectively) (Scheme 4).[16c,d,19] Attempts to cleave the cyclopentenyl olefin of amine **20** with either potassium permanganate or ruthenium tetraoxide were unsuccessful, giving complex mixtures of products. Successful olefin cleavage was realized through the use of ozonolysis conditions. Treatment of amines **20** and **21** with ozone in basic methanol provided direct access to α-methyl β-amino dimethyl esters **22** and **23** in 63 and 49% yield, respectively.[16e,f,20,21] Interestingly, even under the basic reaction conditions, no evidence of epimerization at the α-methyl position was observed.

3. Conclusions

β-Amino diacids and diesters are valuable synthetic intermediates, particularly in the construction of β-lactams. α-Methyl β-amino diesters **22** and **23** were readily accessed in a simple three-step procedure from acylnitroso Diels–Alder cycloadducts **14** and **15**. Treatment of **14** and **15** with copper catalyst-modified methylmagnesium bromide gave *anti*-1,2-cyclopentenyl hydroxamic acids **16** and **17**. Reduction of the hydroxamate N–O bond with titanium(III) chloride followed by ozonolytic cleavage of the cyclopentenyl olefin provided β-amino diesters **22** and **23**. These α-methyl β-amino diesters possess the required relative stereochemistry to serve as important precursors to 1β-methyl carbapenems.



Scheme 4.

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16. (a) Characterization data for **16**: white solid; mp 56–58°C; IR (TF) 3223, 2977, 2930, 1691, 1456, 1395, 1368, 1347, 1253, 1167, 1109, 907, 864, 757, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, $J=7.2$, 3H), 1.47 (s, 9H), 2.47 (m, 1H), 2.65 (m, 1H), 2.99 (m, 1H), 4.26 (dt, $J=7.2$, 8.7 Hz, 1H), 5.55 (m, 1H), 5.62 (m, 1H), 7.38 (s, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 19.01, 28.30, 34.32, 41.61, 66.14, 81.73, 127.61, 135.20, 157.14; HRMS (FAB) calcd for $C_{11}H_{20}NO_3$ $(M+H)^+$ 214.1443, found 214.1448.

(b) Characterization data for **17**: white solid; mp 71–73°C; IR (TF) 3256, 2957, 2926, 2875, 1697, 1456, 1415, 1329, 1271, 1212, 1101, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.99 (d, $J=7.2$, 3H), 2.43 (m, 2H), 2.84 (m, 1H), 4.30 (q, $J=7.5$ Hz, 1H), 5.10 (s, 2H), 5.54 (m, 1H), 5.59 (m, 1H), 7.34 (m, 5H), 9.32 (s, 1H); ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (d, $J=7.2$, 3H), 2.47 (m, 1H), 2.68 (m, 1H), 3.05 (m, 1H), 4.38 (overlapping ddd, $J=7.2$, 7.2, 8.7 Hz, 1H), 5.18 (d, $J=3.0$ Hz, 2H), 5.57 (m, 1H), 5.63 (m, 1H), 7.35 (m, 5H), 7.98 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.89, 34.02, 41.17, 65.55, 66.35, 127.69, 127.75, 127.90, 128.36, 135.04, 136.69, 156.51; ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.79, 34.27, 41.46, 66.12, 67.85, 127.49, 127.87, 128.17, 128.45, 135.07, 135.89, 157.53; HRMS (FAB) calcd for $C_{14}H_{18}NO_3$ $(M+H)^+$ 248.1287, found 248.1292.

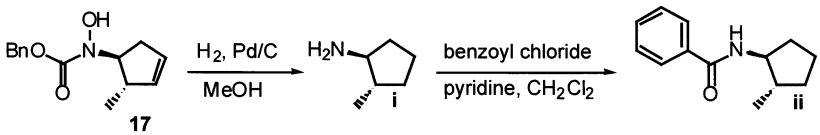
(c) Characterization data for **20**: white solid; mp = 40–43°C; IR (TF) 3343, 2977, 2930, 2870, 1692, 1530, 1502, 1366, 1280, 1248, 1172, 1076, 1042, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, $J=6.9$ Hz, 3H), 1.43 (s, 9H), 2.08 (dd, $J=4.8$, 16.5 Hz, 1H), 2.47 (m, 1H), 2.75 (dd, $J=7.2$, 16.5 Hz, 1H), 3.77 (bs, 1H), 4.67 (bs, 1H), 5.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.60, 28.38, 39.46, 47.52, 57.75, 78.99, 127.56, 135.14, 155.70; HRMS (FAB) calcd for $C_{11}H_{20}NO_2$ $(M+H)^+$ 198.1494, found 198.1509.

(d) Characterization data for **21**: white solid; mp = 59–60°C; IR (TF) 3315, 3032, 2956, 2870, 1685, 1541, 1455, 1279, 1246, 1080, 1034, 974, 760, 709, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, $J=6.9$ Hz, 3H), 2.13 (ddd, $J=1.5$, 4.8, 16.8 Hz, 1H), 2.52 (m, 1H), 2.81 (dd, $J=7.5$, 16.8 Hz, 1H), 3.87 (m, 1H), 4.84 (bs, 1H), 5.10 (s, 2H), 5.62 (s, 2H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.58, 39.55, 47.62, 58.44, 66.63, 120.31, 127.55, 128.07, 128.52, 135.16, 136.73, 156.17; HRMS (FAB) calcd for $C_{14}H_{18}NO_2$ $(M+H)^+$ 232.1338, found 232.1348.

(e) Characterization data for **22**: clear oil; IR (TF) 3372, 2980, 1738, 1726, 1530, 1502, 1440, 1367, 1248, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, $J=7.5$ Hz, 3H), 1.41 (s, 9H), 2.53 (m, 2H), 2.78 (m, 1H), 3.67 (s, 6H), 4.15 (m, 1H), 5.20 (d, $J=9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.88, 28.28, 36.52, 43.16, 49.56, 51.72, 51.78, 79.49, 155.15, 171.75, 174.58; HRMS (FAB) calcd for $C_{13}H_{24}NO_6$ $(M+H)^+$ 290.1604, found 290.1613.

(f) Characterization data for **23**: clear oil; IR (TF) 3351, 2953, 1734, 1522, 1457, 1437, 1238, 1205, 1044, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.21 (d, $J=7.5$ Hz, 3H), 2.58 (m, 2H), 2.83 (m, $J=7.5$ Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 4.23 (m, 1H), 5.09 (s, 2H), 5.47 (d, $J=9.5$ Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.01, 36.32, 43.11, 50.24, 51.77, 52.60, 66.85, 128.03, 128.11, 128.50, 136.50, 155.78, 171.65, 174.46; HRMS (FAB) calcd for $C_{16}H_{22}NO_6$ $(M+H)^+$ 324.1447, found 324.1453.

17. The *anti*-1,2-stereochemical assignment of the major product **17** was proven through the synthesis of known *trans*-2-methyl-cyclopentyl-benzamide from hydroxamic acid **17**. *anti*-1,2-Hydroxamic acid **17** was exposed to hydrogenation conditions to remove the Cbz group and reduce the N–O bond and cyclopentenyl olefin. The resulting cyclopentyl amine **i** was treated with benzoyl chloride to give the benzamide derivative **ii**. The melting point of **ii** (114–115°C) was consistent with the literature value (116°C).[18] The melting point of *cis*-2-methyl-cyclopentyl-benzamide is 85°C.



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21. Treatment of *O*-benzyl hydroxamate **18** under these ozonolysis conditions resulted in only a modest yield (31%) of the corresponding diester **19**.