Chemoselectivity in the Pd-Catalyzed Cyclization of 1,6-Enynes and Proof of the Relative Configuration of the New Stereogenic Centers

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Received March 23, 2001; Accepted May 4, 2001

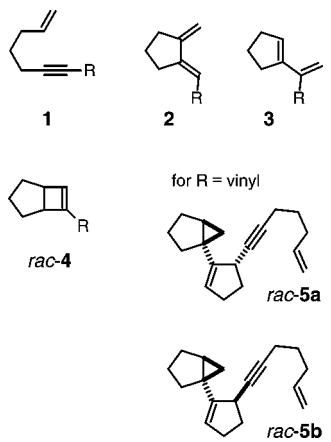
Dedicated to Professor Paul Binger on the occasion of his 70th birthday

Abstract: The dimerization of dienyne **6** with a palladole catalyst readily provides the bicyclic enyne *rac*-**7**. A second cyclization of the 1,6-enyne substructure in *rac*-**7** works best with a hydropalladation catalyst and delivers *rac*-**8**. Diels-Alder reactions of the latter finally lead to a crystalline product *rac*-**12**. A crystal structure analysis of *rac*-**12** allowed the determination of the relative configuration of all stereogenic centers formed in the dimerization of **6**.

Keywords: chemoselectivity; cyclization; diastereoselectivity; Diels-Alder reaction; palladium

Introduction

Palladium-catalyzed cyclizations of 1,6-enynes **1** have become important synthetic tools for organic synthesis.[1] Depending on the substituents R and the nature of the catalyst, in absence of other substrates different routes like the "normal" enyne cyclization leading to dimethylenecyclopentanes **2**,[2] the enyne metathesis leading to vinylcyclopentenes **3**,[3] and the formation of bicyclo[3.2.0]heptenes **4**[4] and cyclopentenylbicyclo[3.1.0]hexanes **5**[5] have been observed. The novelty of the last reaction led us to try to understand its mechanism — a process thwarted by the inability to establish the stereochemistry of the adduct itself.



Scheme 1. Products of the Pd-catalyzed cycloisomerization of different 1,6-enynes.

The latter reaction is an unprecedented dimerization of **1**. Interestingly, the product **5** still contains a 1,6-enyne substructure — a structural feature that lends itself to further palladium-catalyzed reactions. Furthermore, only one of the two conceivable diastereomers **5a** and **5b** was observed. Extensive NMR measurements allowed the assignment of all signals within the bicyclohexyl and the cyclopentenyl parts but not a stereochemical correlation between these two subunits. Therefore, assignment of the products to either **5a** or **5b** was impossible. As none of the other compounds of type **5** that we had synthesized was crystalline, an X-ray crystal structure analysis was also not possible. In this paper, the further palladium-catalyzed reaction of enyne **5** and its application for establishing the relative stereochemistry of the novel initial cyclodimerization is outlined.

Results and Discussion

The dialkyl malonate **6** was subjected to 0.1 mol % $TCPC^{HFB}$ in benzene at 60 °C. After 30 hours, **7** was formed in a highly selective reaction. Only 3% of the

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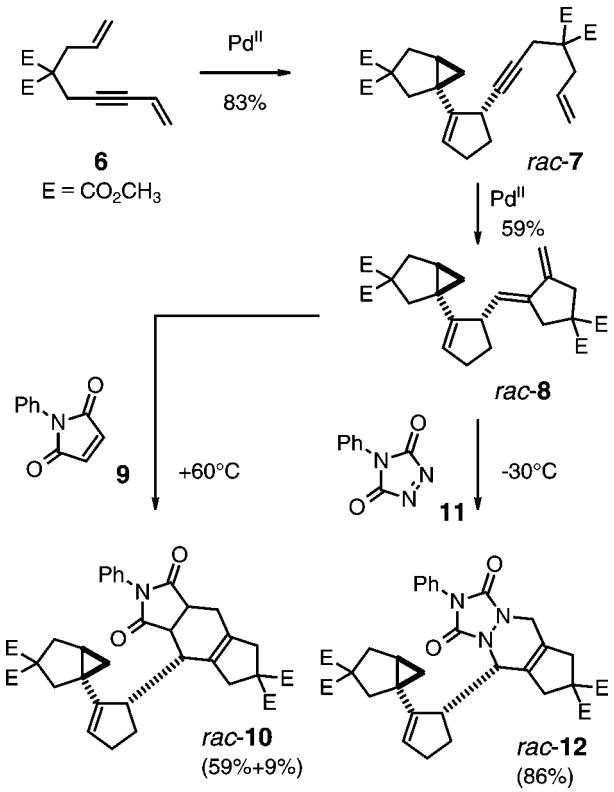
starting material **6** could be reisolated. Neither constitutional isomers nor stereoisomers of **7** could be detected. The next cycloisomerization started at 80 °C and was much slower. After 166 hours, 59% of **8** could be obtained. A one-pot conversion of **6** was observed with 10 mol % the $TCPC^{TFE}$/tri-*o*-tolyl phoshite catalyst; after 128 hours at 80 °C, 57% of **8** was formed. The synthesis of the latter was much more efficient starting from **7** and applying different conditions for the second cyclization. Thus, 0.5 mol % of $Pd_2dba_3{\cdot}CHCl_3$/tri-*o*-tolylphosphane/acetic acid[6] at 62 °C after 43 hours converted enyne **7** into **8** in 83% isolated yield in a clean reaction (higher catalyst loads reduced the yield of **8**). Subjecting **7** to 5 mol % of $Pd(OAc)_2$ for 8 hours at 60 °C provided only 35% of **8**.

In **7**, the alkyne bears an isopropyl-like substituent. On the other hand, substrates like **13** where the alkyne is attached to a *tert*-butyl-like substituent fail in the enyne cyclization.



Scheme 2. Synthesis of *rac*-**8**, *rac*-**10** and *rac*-**12**.

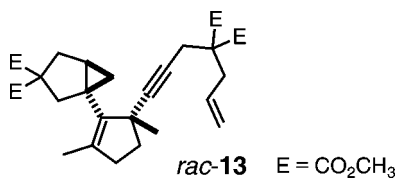


Figure 1. Unreactive 1,6-enyne *rac*-**13**.

The inability to assign the relative stereochemistry of **5** and related substrates made it desirable to obtain an X-ray crystal structure. Unfortunately, **8** also was an oil. The 1,3-diene subunit, however, would allow Diels-Alder reactions with polar dienophiles to yield products that might be crystalline. First, the Diels-Alder adduct of **8** and *N*-phenylmaleinimide **9**[7] was formed at 60 °C. Two different diastereomers of **10** were obtained (ratio 6:1), but their melting points were below 60 0°C and we could not get crystals of good quality.

On the other hand, the Diels-Alder dienophile **11**[8] readily reacted with **8** at –30 °C to stereoselectively (by NMR) provide **12** as a foam. Crystals suitable for a X-ray crystal structure analysis were obtained upon recrystallization from diethyl ether at room temperature. The solid-state structure of **12** is shown in Figure 2[9] and reveals the relative configuration of the stereogenic centers formed in the transformation of **6** to **7** from formerly sp^2 and sp configurated carbon atoms. This analysis also proves the structural assignments for **7** and **8**. We never observed an epimerization under conditions like those applied for the conversion of **7** to **8**.[10]

Scheme 3 outlines a mechanistic rationale. The reaction is believed to involve initial metallacycle formation followed by a metallacyclopentene to metallavinylcyclopropane rearrangement. The stereochemistry is then set in the addition of the dienophile to metallavinylcyclopropane **14**. Initial coordination as in **15** may set the stage for the cycloaddition to produce metallacyclohexene **16**, the precursor of *rac*-**7**. On the other hand, the opposite facial selectivity with respect to the vinyl group invokes *epi*-**15** to form *epi*-**16**. In both cases, steric interactions disfavor this path and thus disfavor formation of *epi*-**7**.

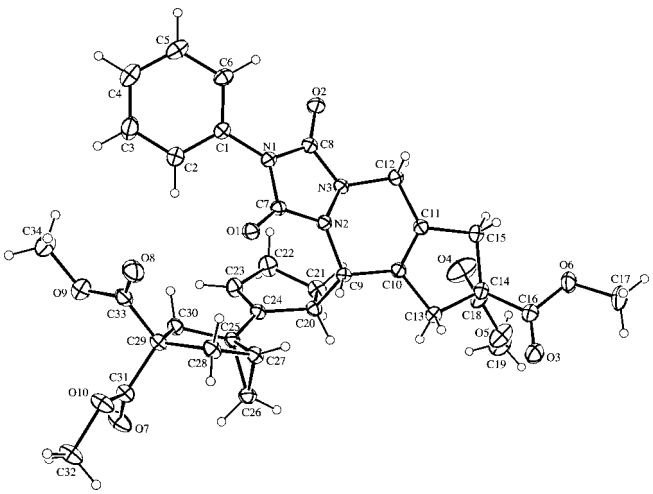
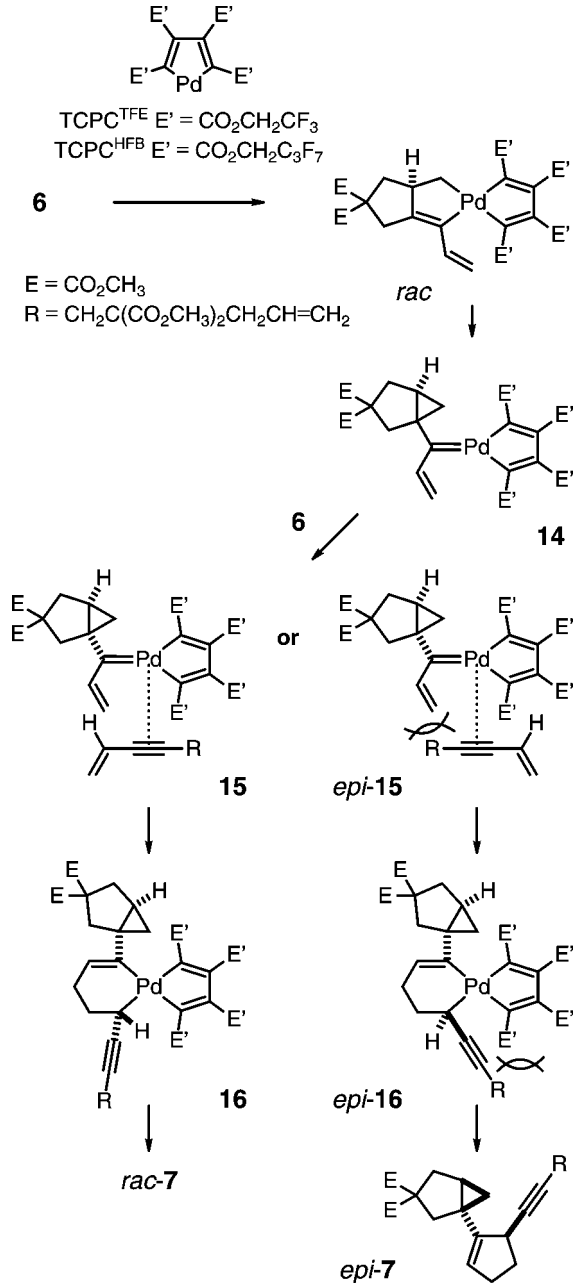


Figure 2. Perspective view (ORTEP) of compound *rac*-**12** showing the atomic numbering scheme.



Scheme 3. A mechanistic rationale.

The Diels-Alder reactions also proceed with excellent facial selectivity with respect to the diene.[11] Thus, only one diastereomer is generated using triazolinedione **11** as dienophile as depicted in *rac*-**12**. Assuming an *endo* transition state for the major diastereomer of the Diels-Alder adduct with dienophile **9**, then the relative stereochemistry depicted in *rac*-**10** can be assigned to the major cycloadduct. It is quite striking that six stereocenters can be created with very good diastereoselectivity in this atom economical reaction sequence involving 1) a metal-catalyzed novel cycloaddition, 2) a metal-catalyzed cycloisomerization, and 3) a thermal cycloaddition.

Conclusion

We now have proven the stereochemical assignments for compounds **7** reported previously[5] and shown that products of type **5a** are formed in the Pd-catalyzed dimerization of substrates of type **1**. A second enyne cyclization is possible for compounds of type **7** while the additional steric hinderance in **13** prevents such a reaction.

Experimental Section

1-{5-[4,4-Bis(methoxycarbonyl)hept-6-en-1-ynyl]-cyclopent-1-enyl}bicyclo[3.1.0]hexane-3,3-dicarboxylic Acid Dimethyl Ester (7)

A mixture of 2-allyl-2-prop-2-ynylmalonic acid dimethyl ester (**6**; 473 mg, 2.00 mmol) and TCPC^{HFB} (2.13 mg, 2.00 μmol, 0.1 mol %) in benzene (8 mL) was heated to 60 °C. After 30 hours the solvent was removed under vacuum. Column chromatography (SiO_2, hexane/ethyl acetate = 4/1) provided **7** as a colorless oil; yield: 410 mg (87%); R_f = 0.30 (hexane/ethyl acetate = 3/1); IR (neat, NaCl): ν = 3004, 2955, 2849, 1739, 1733, 1642, 1436, 1325, 1290, 1251, 1218, 1204, 1178, 1097, 1071, 966, 921, 816, 791, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.60 (ddt, *J* = 17.0 Hz, 10.0 Hz, 7.5 Hz, 1 H), 5.48 (m, 1 H), 5.12 (ddm, *J* = 17.0 Hz, 2.1 Hz, 1 H), 5.09 (ddm, *J* = 10.0 Hz, 2.1 Hz, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.70 (s, 3 H), 3.67 (s, 3 H), 3.13 (br m, 1 H), 2.74 (m, 2 H), 2.71 (m, 1 H), 2.67 (m, 1 H), 2.63 (dd, *J* = 13.7, 1.4 Hz, 1 H), 2.57 (d, *J* = 13.7 Hz, 1 H), 2.55 (m, 1 H), 2.49 (dd, *J* = 13.7 Hz, 4.9 Hz, 1 H), 2.33–2.45 (m, 1 H), 2.21–2.27 (m, 1 H), 2.03–2.18 (m, 1 H), 1.85 (m, 2 H), 0.80 [ddm (W-type coupling involved), 1 H], 0.36 (dd, *J* = 5.8 Hz, 4.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 172.6, 170.7 (2), 145.0, 132.2, 125.1, 119.7), 85.9, 75.4, 58.6, 57.2, 52.9, 52.7, 52.5 (2), 39.3, 36.5, 36.2, 36.0, 33.2, 30.8, 29.2, 23.5, 23.0, 15.5; MS calcd. for $C_{26}H_{32}O_8$: 472.2097; found: 472.2080; *m/z* = 472 (M^+, 18%), 353 (29), 321 (29), 300 (51), 293 (44), 241 (81), 240 (56), 233 (30), 209 (29), 203 (26), 182 (25), 181 (100), 180 (27), 179 (37), 168 (26), 167 (51), 166 (29), 165 (47), 155 (42), 153 (33), 145 (30), 143 (43), 141 (39), 129 (32), 128 (37), 115 (37), 113 (41), 91 (39); anal. calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83; found: C, 65.99; H, 6.84.

1-{5-[4,4-Bis(methoxycarbonyl)-2-methylenecyclopent-(*E*)-ylidenemethyl]cyclopent-1-enyl}-bicyclo[3.1.0]hexane-3,3-dicarboxylic Acid Dimethyl Ester (8)

A mixture of **7** (410 mg, 868 μmol), $Pd_2dba_5{\cdot}CHCl_5$ (4.49 mg, 4.34 μmol, 0.5 mol %), tri-*o*-tolylphosphane (5.30 mg, 17.4 μmol, 2 mol %), and acetic acid (0.52 mg, 8.68 μmol, 1 mol %) in benzene (5 ml) was heated at 62 °C for 43 hours. The solvent was removed under vacuum. Column chromatography (SiO_2, hexane/ethyl acetate = 5/1) provided **8** as a colorless oil; yield: 340 mg (83%); R_f = 0.33 (hexane/ethyl acetate = 3/1); IR (neat, NaCl): ν = 2954, 1735, 1435, 1288, 1251, 1203, 1174, 1116, 1097, 1071, 965, 946, 881 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (dt, *J* = 10.4 Hz, 2.4 Hz, 1 H), 5.56 (m, 1 H), 5.24 (t, *J* = 2.1 Hz, 1 H), 4.84 (br s, 1 H), 3.74 (s, 3 H), 3.74 (s, 3 h), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.21 (m, 1 H), 3.01 (m, 3 H), 2.70 (d, *J* = 13.5 Hz, 1 H), 2.59 (m, 2 H), 2.46 (dd, *J* = 13.7 Hz, 4.6 Hz, 1 H), 2.37 (m, 1 H), 2.26–2.28 (m, 1 H), 2.05–2.18 (m, 1 H), 1.60 (m, 1 H), 1.50 (m, 1 H), 0.87 (m, 1 H), 0.70 (ddm, *J* = 8.4 Hz, 5.8 Hz, 1 H), 0.33 (dd, *J* = 5.8 Hz, 4.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 172.7, 172.1, 172.0, 147.6, 145.2, 134.8, 126.5, 125.4, 103.4, 58.5, 57.6, 52.9, 52.7, 46.2, 41.2, 39.5, 37.5, 36.2, 31.8, 30.9, 29.5, 23.3, 15.2. MS: calcd. for $C_{26}H_{32}O_8$: 472.2097; found: 472.2094; *m/z* = 472 (M^+, 74%), 413 (39), 412 (50), 381 (42), 353 (63), 352 (38), 321 (48), 293 (73), 275 (27), 263 (29), 262 (40), 261 (53), 233 (46), 215 (80), 214 (31), 203 (82), 202 (68), 201 (49), 181 (26), 179 (25), 165 (36), 155 (64), 153 (27), 151 (30), 145 (31), 143 (100), 142 (29), 141 (35), 129 (43), 128 (47), 117 (46), 115 (47), 113 (35), 91 (62), 77 (26); anal. calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83; found: C, 66.33; H, 6.64.

4-{2-[3,3-Bis(methoxycarbonyl)bicyclo[3.1.0]hex-1-yl]cyclopent-2-enyl}-1,3-dioxo-2-phenyl-2,3,3a,4,5,7,8,8a-octahydro-1*H*-cyclopenta[*f*]isoindole-6,6-dicarboxylic Acid Dimethyl Ester (10)

To compound **8** (68.0 mg, 144 μmol) in $CDCl_3$ (1.5 mL) was added *N*-phenylmaleinimide (**9**; 24.9 mg, 144 μmol). After heating to 60 °C for 57 hours, the solvent was removed under vacuum. Column chromatography (SiO_2, hexane/ethyl acetate=2/1) provided **10** as a colorless powder; yield: 51.4 mg (55%); R_f = 0.70 (hexane/ethyl acetate=1/1). In addition, a second diastereomer of **10** was obtained; yield:8.6 mg (9%); R_f = 0.60 (hexane/ethyl acetate=1/1).

Major diastereomer of 10: mp 56–59 °C; IR (neat, NaCl): ν = 2954, 2928, 2853, 2361, 1732, 1714, 1500, 1455, 1435, 1383, 1256, 1201, 1174, 1072, 915, 756, 733, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.46 (m, 3 H), 7.21–7.27 (m, 2 H), 5.40 (br s, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 2.94–3.36 (m, 8 H), 2.52–2.77 (m, 4 H), 2.36–2.43 (m, 3 H), 1.95–2.24 (m, 3 H), 1.57–1.61 (m, 1 H), 0.70 (m, 1 H), 0.47 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9 (s), 176.6 (s), 173.4 (s), 172.7 (s), 172.5 (2 s), 146.4 (s), 136.9 (s), 132.8 (s), 132.2 (s), 129.2 (2 d), 128.5 (d), 126.6 (2 d), 126.4 (d), 59.4 (s), 58.2 (s), 52.9 (q), 52.8 (3 q), 47.4 (d), 43.4 (t), 43.3 (d), 42.1 (t), 41.0 (d), 40.0 (t), 38.8 (d), 35.9 (t), 30.7 (t), 28.6 (t), 24.4 (t), 23.6 (d), 19.0 (t) (one quaternary alkyl carbon is hidden by signal-overlap, but visible in acetonitrile-d_6); HRMS: calcd for $C_{36}H_{39}NO_{10}$, (M^+): 645.2574; found: 645.2564; *m/z* = 645 (M^+, 3%), 615 (1.8), 614 (5), 554 (2.7), 553 (2.3), 522 (1.4), 494 (1.4), 446 (1.4), 383 (15), 323 (38), 264 (27), 263 (100), 203 (87), 143 (22).

Minor diastereomer of 10: IR (neat, NaCl): ν = 2954, 2928, 2854, 1733, 1714, 1500, 1456, 1435, 1382, 1256, 1202, 1174, 1072, 914, 734, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.51 (m, 5 H), 5.30 (br s, 1 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 2.05–3.39 (m, 18 H), 1.68 (m, 1 H), 0.70 (m, 1 H), 0.52 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2 (s), 177.8 (s), 173.5 (s), 172.7 (3 s), 147.5 (s), 133.1 (s), 132.3 (s), 129.4 (2 d), 128.7 (d), 126.3 (2 d), 125.2 (d), 58.9 (s), 57.7 (s), 52.9 (q), 52.8 (q), 52.8 (q), 52.7 (q), 47.3 (d), 45.0 (t), 43.8 (t), 43.4 (d), 39.6 (t), 38.6 (d), 36.9 (d), 36.1 (t), 31.6 (t), 28.3 (s), 26.7 (t), 23.8 (d), 21.8 (t), 18.8 (t), some signals were not visible due to the small amount; HRMS: calcd for $C_{36}H_{39}NO_{10}$ (M^+): 645.2574; found: 645.2582; *m/z* = 645 (M^+, 3%), 383 (15), 323 (40), 322 (10), 264 (21), 263 (100), 231 (16), 204 (17), 203 (97), 199 (13), 175 (10), 171 (10), 143 (31), 117 (11), 115 (14).

5-[2-(3,3-Bismethoxycarbonylbicyclo[3.1.0]hex-1-yl)cyclopent-2-enyl]-1,3-dioxo-2-phenyl-2,3,6,9-tetrahydro-1*H*,5*H*,8*H*-cyclopenta[*d*][1,2,4]triazolo[1,2-*a*]pyridazine-7,7-dicarboxylic Acid Dimethyl Ester (12)

To a solution of **8** (340 mg, 720 mmol) in chloroform (3 mL) at –30 °C was added a solution of *N*-phenyl-1,2,4-triazolinedione (**11**; 126 mg, 720 mmol)) in chloroform (6 mL) dropwise. Finally, the solution was warmed to room temperature and the solvent removed under vacuum. Column chromatography (SiO_2, hexane/ethyl acetate = 1/1) provided **12** as a colorless oil; yield: 399 mg (86%); R_f = 0.58 (hexane/ethyl acetate = 1/1). The material does not crystallize from solvents like chloroform or dichloromethane (even after long periods in the freezer), but when put on the pump after removal of these solvents, a hard foam is formed (mp 83–85 °C from $CHCl_3$). Crystals could be obtained from ether (slow cooling from a hot, saturated solution to room temperature) (mp 160.5–162 °C to turbid drops which became clear at 170–173 °C); IR (neat, NaCl): ν = 3003, 2954, 2854, 1730, 1504, 1433, 1257, 1204, 1174, 1129, 1100, 1072, 983, 915, 764, 733, 692, 648 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.30 (m, 5 H), 5.49 (br s, 1 H), 4.80 (br s, 1 H), 4.32 (d, *J* = 16.2 Hz, 1 H), 4.00 (d, *J* = 16.2 Hz, 1 H), 3.78 (s, 3 H), 3.78 (s, 3 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.03–3.22 (m, 4 H), 2.88 (br m, 1 H), 2.56–2.77 (m, 4 H), 2.17–2.21 (m, 2 H), 1.87–1.95 (m, 2 H), 1.62–1.66 (m, 1 H), 0.85 (m, 1 H), 0.48 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (s), 172.2 (s), 171.7 (s), 171.7 (s), 154.0 (s), 149.1 (s), 145.2 (s), 131.6 (s), 130.9 (s), 129.2 (s), 129.1 (2 d), 128.0 (d), 127.6 (s), 126.7 (d), 125.5 (2 d), 58.8 (s), 58.2 (s), 53.4 (d), 53.0 (2 q), 52.6 (2 q), 48.2 (d), 45.3 (t), 40.8 (t), 40.7 (t), 39.3 (t), 35.5 (t), 30.4 (t), 28.9 (s), 26.1 (t), 24.7 (d), 17.0 (t). MS: calcd. for $C_{34}H_{37}N_3O_{10}$: 647.2479; found: 647.2487; *m/z* = 647 (M^+, 0.2%), 386 (5), 385 (27), 384 (100), 383 (3), 325 (8), 324 (38), 263 (4), 205 (7), 203 (4), 162 (3), 143 (5), 118 (5), 91 (3); anal. calcd. for $C_{34}H_{37}N_3O_{10}$: C, 63.05; H, 5.76; N, 6.49; found: C, 63.08; H, 5.98; N, 6.26.

Acknowledgements

We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. A.S.K.H. is indebted to the Deutsche Forschungsgemeinschaft for fellowship support (Ha 1932/1–1 and Ha 1932/1–2). Mass spectra were generously provided by the University of California – San Francisco Mass Spectrometry Center sponsored by the NIH Division of Research Resources.

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[9] Carried out by Dr. R. G. Ball. Compound $C_{34}H_{37}N_5O_{10}$ (**12**), $M_r = 647.688$, triclinic, $P\bar{1}$, $a = 12.871(1)$, $b = 12.8758(8)$, $c = 11.1349(6)$ Å, $\alpha = 101.066(5)$, $\beta = 101.960(6)$, $\gamma = 112.7(3)°$ $V = 1587(5)$ Å^3, $Z = 2$, $D_x = 1.355$ g cm^{-3}, Cu K_α monochromatized radiation, $\mu = 0.80$ mm^{-1}, $F(000) = 1368$, $T = 293$ K. Data were collected on a Enraf-Nonius CAD4 diffractometer to a θ limit of 70° which yielded 6020 measured (5823 unique) reflections. There are 4737 unique, observed reflections (with $I \geq 3\sigma(I)$ as the criterion for being observed) out of the total measured. The structure was solved by direct methods (SHELXS-86) and refined using full-matrix least-squares on F (SDP-PLUS). The final model was refined using 425 parameters and the observed data. All non-hydrogen atoms were refined with anisotropic thermal displacements; the hydrogens are included at their calculated positions, assuming ideal geometry, and allowed to ride on the attached atom. The final agreement statistics are: $R = 0.058$, $wR = 0.066$, $S = 3.87$ with $(\Delta/\sigma)_{max} = 0.03$. The least-squares weights were defined using $1/\sigma^2(F)$. The maximum peak height in a final difference Fourier map is 0.74(5) e·Å^{-3} and this peak is without chemical significance. All bond distances and angles are within the expected ranges. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-158004 (compound **12**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44 1233/336–033; e-mail: deposit@ccdc.cam.ac.uk].

[10] In flash-vacuum-thermolysis reactions we could prepare such epimers and thus compare their NMR data with the data of **7** and **8**.

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