Asymmetric Hetero Diels−Alder as an Access to Carbacephams

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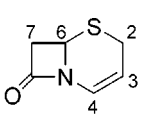
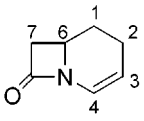
Abstract: A short and efficient asymmetric synthesis of the (6*R*,7*S*)-7-*tert*-butoxycarbonylamino-2-ketocarbacepham is described. The key step involves the hetero Diels−Alder reaction of the benzylimine derived from the enantiomer of Garner's aldehyde with Danishefsky's diene.

The bacterial resistance to cephalosporins (cephems), caused by their widespread use during the past decades,[1] has motivated a growing interest in the preparation and biological evaluation of the new types of β-lactams. In this sense, carbacephalosporins (carbacephems) are known to exhibit antibiotic activity and increased chemical stability compared to cephalosporins.[2] In particular, Loracarbef is the first example of this new class of antibiotics that has been marketed.[3]

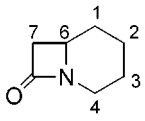
Carbacephems are generally obtained from functionalized carbacephams.[4] In this sense, the significance of carbacephams is due not only to the role they play as precursors of carbacephems but also to the fact that they are interesting compounds to investigate the biological behavior of β-lactam antibiotics.[5]



3-cephems



3-carbacephems

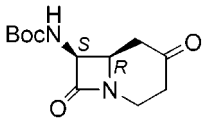


carbacephams

Most synthetic approachs to carbacephem or the carbacepham ring system involve appending a six-membered ring onto a β-lactam, using different reactions.[6] Nevertheless, the construction of the six-membered ring followed by the formation of the β-lactam ring has only been found in a few examples of carbacepham synthesis.[4e,5a,7]

Using the above-mentioned strategy, we describe here an efficient approach to asymmetric synthesis of the carbacepham **1**, using as key step the hetero Diels−Alder reaction (HDA) of the benzylimine derived from the enantiomer of Garner's aldehyde with Danishefsky's diene.

The piperidine ring formed in the HDA possesses the appropriate stereochemistry at the stereogenic center, which would allow the *cis* substitution at C-6 and C-7 required in the carbacepham system, according to the literature, and directly related to the biological activity of the carbacephems.[2a] Moreover, the carbonyl group at C-2 can be conveniently used to prepare further carbacephem or carbacepham derivatives.



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Because of the importance of functionalized piperidines, contained in numerous physiologically active compounds,[8] a considerable synthetic effort has been made toward the preparation of these systems.[9] In this context, the HDA of C−N double bonds with carbon dienes is probably one of the most efficient routes toward substituted piperidines.[9,10]

However, the asymmetric version of this reaction has been developed very lately, in the past decade, and has been recently reviewed.[11] In this sense, there are few examples of asymmetric HDA with unactivated chiral imines in which the chiral matrix is the carbonyl moiety; therefore, to the best of our knowledge, we report here the first example of an asymmetric HDA with an unactivated imine derived from a chiral α-aminoaldehyde.

Imine **2** was prepared from the enantiomer of Garner's aldehyde[12] and benzylamine in the presence of anhydrous magnesium sulfate, conditions where enantiomerization at the stereogenic center is not observed.[13] This crude imine **2** reacts with Danishefsky's diene, in the presence of a Lewis acid catalyst and dichloromethane as solvent,

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Scheme 1. HDA Reaction of Imine 2 with Danishefsky's Diene

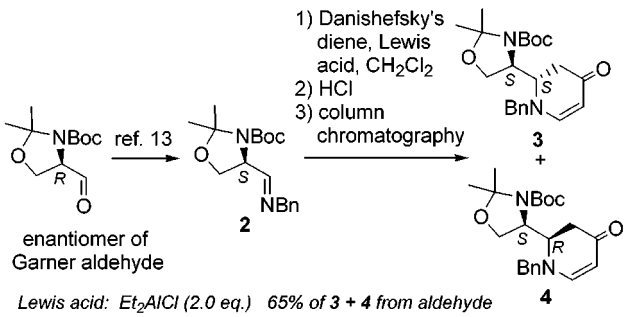


Table 1. HDA Reaction of Imine 2 with Danishefsky's Diene

entry	LA (equiv)[a]	*T* (°C)	*t* (h)	yield (%)[b]	**3**/**4**[c]
1	$ZnCl_2$ (0.7)	0	6	28	38/62
2	$ZnCl_2$ (1.0)	−50	28	20	36/64
3	$ZnCl_2$ (1.2)	−40	48	29	21/79
4	Et_2AlCl (1.0)	0	72	38	41/59
5	Et_2AlCl (1.0)	−20	24	41	26/74
6	Et_2AlCl (1.0)	−40	26	57	25/75
7	Et_2AlCl (1.5)	−40	72	34	24/76
8	Et_2AlCl (2.0)	−40	17	65	17/83
9	$EtAlCl_2$ (1.0)	−40	48	55	19/81
10	$EtAlCl_2$ (2.0)	−40	15	57	20/80

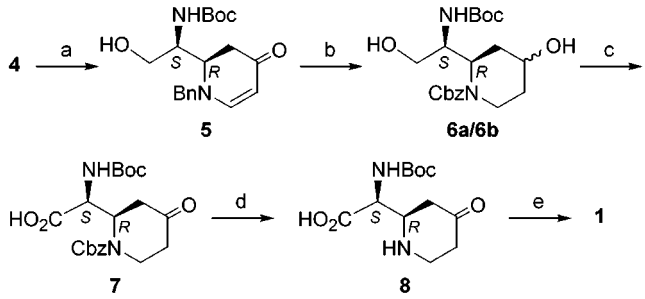
[a] LA (equiv): Lewis acid (equivalents). [b] Determined after acid hydrolysis and further purification by silica gel column chromatography and calculated from enantiomer of Garner's aldehyde. [c] Measured by ^{1}H NMR at the vinylic protons and corroborated by HPLC. (Column: Hypersil ODS, 5 μm, 250 mm × 2.1 mm. Detection: UV 198 nm. Flow: 0.35 mL/min. Eluent: MeOH−H_2O 55/45).

to give after acid hydrolysis the corresponding hetero Diels−Alder adducts **3** and **4**, in different proportions depending on the temperature and the catalyst used, as depicted in Scheme 1 and Table 1.

On the basis of preliminary results of hetero Diels−Alder reactions between Danishefsky's diene and various chiral imines carried out by one of us to synthesize pipecolic acid derivatives,[14] we assayed the cycloaddition with different proportions of $BF_3{\cdot}Et_2O$, $ZnCl_2$, ZnI_2, Et_2AlCl, or $EtAlCl_2$ as Lewis acids and a range of temperatures between −50 and 0 °C. With $BF_3{\cdot}Et_2O$ or ZnX_2 (2 equiv) the reaction did not progress. The best results of diastereoselectivity and yield were achieved when 2 equiv of Et_2AlCl were used at −40 °C (entry 8, Table 1).

Once the major cycloadduct **4** in enantiomerically pure form had been obtained, its absolute configuration was determined by X-ray crystal structure analysis.[15] Starting from this compound **4** and using five steps, carbacepham **1** was achieved carrying out the following synthetic strategy. Initially, we attempted the cleavage of the *N*,*O*-acetal using various mild acid conditions but in all cases the *N*-Boc group was hydrolyzed. Therefore, the treatment of compound **4** with 4 N HCl in a mixture of THF−H_2O at 25 °C gave the corresponding 1,2-amino alcohol, whose amino group was again protected by the action of $(Boc)_2O$ in a basic medium to give compound **5** with an overall yield of 95% from **4**.

Scheme 2. Synthesis of Carbacepham 1 from Cycloadduct 4[a]



[a] Reagents and conditions: (a) (i) 4 N HCl, THF−H_2O (3:1), 25 °C; (ii) $(Boc)_2O$, $Na_2CO_3{\cdot}10H_2O$, THF−H_2O (5:1), 25 °C, 95%; (b) (i) Raney Ni, MeOH, 50 °C; (ii) CbzCl, $Na_2CO_3{\cdot}10H_2O$, THF−H_2O (5:1), 25 °C, 88%; (c) Jones oxidation, 90%; (d) H_2, Pd−C, MeOH, 25 °C, 98%; (e) 2-chloro-*N*-methylpyridinium iodide, TEA, MeCN, 70 °C, 45%.

The concomitant hydrogenation of the double bond and the hydrogenolysis of the benzyl group in compound **5** were achieved in one step using Raney Ni in MeOH. Under these conditions, the ketone group was also reduced to the corresponding mixture of alcohols. Subsequent protection of the amino group, carried out with CbzCl in the presence of sodium carbonate, gave the mixture of alcohols **6a**/**6b** with an overall yield of 88% from **5**, in a ratio 3:1 determined by ^{1}H NMR (Scheme 2).

The mixture of alcohols **6a**/**6b** was treated with the Jones reagent, and the sole product **7** was obtained, with a yield of 90%, by oxidation of the primary alcohol to the carboxylic acid and the secondary alcohols to the ketone group. The direct precursor of the carbacepham **1**, the β-amino acid **8**, was obtained after deprotection of the benzyl carbamate group of compound **7** by hydrogenation in the presence of palladium−carbon as catalyst (Scheme 2).

With the β-amino acid **8** in hand, the next step was the cyclization of the amino acid to form the bicyclic β-lactam **1**. Although several methods to accomplish the intramolecular cyclization of amino acids to lactams have been described, in which either the carboxyl or the amino group must be activated, really very few have given good results in the case of β-lactams.[4e,7] In this sense, a common method for activating carboxylic acids toward nucleophilic substitution is to use Mukaiyama's reagent,[16] 2-chloro-*N*-methylpyridinium iodide, which has also been successfully used to generate the β-lactam ring.[4e,7,11,17] Therefore, in our case, applying to the β-amino acid **8** Mukaiyama's reagent as coupling agent and triethylamine (TEA) as base, we obtained the required carbacepham **1** with a 45% yield after column chromatography (Scheme 2).

Azetidinone **1** was isolated as a stable crystalline solid, and we could obtain a single crystal suitable for X-ray analysis. Thus, the X-ray crystal structure of **1** confirms the absolute configuration at the sterogenic centers.[15]

In summary, we have developed a brief and straightforward synthesis of the functionalized carbacepham **1**, which will be used as precursor of different carbacephems. The carbacepham core, the bicyclo[4.2.0]octane ring

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system, has been prepared by an unusual synthetic route, which first involves the generation of the six-membered ring, followed by the construction of the β-lactam ring. One of the stereogenic centers of the system comes from the starting material, the chiral imine derived from the enantiomer of Garner's aldehyde, and the second one is created in the asymmetric hetero Diels−Alder reaction of this imine with Danishefsky's diene.

Experimental Section

General Procedures. Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. The chemical reagents were purchased from the Aldrich Chemical Co. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Kieselgel 60 (230−400 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, concentrated under reduced pressure using a rotary evaporator. IR spectra ν_{max} (cm^{-1}) are given for the main absorption bands. NMR spectra were recorded at 300 (^1H) and at 75 (^{13}C) MHz and are reported in ppm downfield from TMS. Mass spectra were obtained by electrospray ionization (ESI).

(4*S*,2′*S*)-4-(1′-Benzyl-4′-oxo-1′,2′,3′,4′-tetrahydropyridin-2′-yl)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine (3) and (4*S*,2′*R*)-4-(1′-Benzyl-4′-oxo-1′,2′,3′,4′-tetrahydropyridin-2′-yl)-3-*tert*-butoxycarbonyl-2,2-dimethyloxazolidine (4). To a suspension of anhydrous $MgSO_4$ (200 mg) in CH_2Cl_2 (10 mL) was added, at 25 °C under an inert atmosphere of argon, a solution of aldehyde (*R*)-3-*tert*-butoxycarbonyl-4-formyl-2,2-dimethyloxazolidine (enantiomer of Garner's aldehyde) (0.80 g, 3.5 mmol) and benzylamine (0.37 g, 3.5 mmol) in CH_2Cl_2 (40 mL). After 2 h of stirring at the same temperature, the solution corresponding to the crude imine **2** was filtered under an atmosphere of argon over a Schlenk containing molecular sieves (4 Å), which was then cooled to −40 °C, and a 1 M solution of Et_2AlCl in hexane (7.0 mL, 7.0 mmol) was added. After 5 min of stirring at −40 °C, Danishefsky's diene (0.90 g, 5.2 mmol) was added, and the mixture was stirred for 17 h at the same temperature. The reaction mixture was extracted with a 1 N aqueous solution of HCl (10 mL), and the organic phase was dried (Na_2SO_4), filtered, and concentrated to give an oily residue corresponding to cycloadducts **3** and **4** (523 mg, 65% from enantiomer of Garner's aldehyde) in a ratio of 1:4, respectively. These cycloadducts were separated by silica gel column chromatography (hexane−ethyl acetate, 3:7) to give 0.71 g of compound **4** (52%) as a white solid and 0.17 g of compound **3** (13%) as an oil. Compound **3**: Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.28; H, 7.77; N, 7.21. $[\alpha]^{25}_D$ (*c* 1.41, MeOH) −38.3. IR (CH_2Cl_2) ν (cm^{-1}): 1691, 1641. ^1H NMR ($CDCl_3$) δ: 1.25−1.75 (m, 15H), 2.11−2.43 (m, 1H), 2.55−2.73 (m, 1H), 3.61−4.21 (m, 4H), 4.45 (s, 2H), 4.47−4.95 (m, 1H), 7.01−7.14 (m, 1H), 7.15−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.4, 24.1, 26.2, 28.3, 36.5, 37.5, 55.4, 56.6, 59.0, 60.0, 64.4, 65.0, 80.6, 94.3, 97.2, 98.4, 127.1, 128.1, 128.8, 136.6, 152.0, 153.4, 154.4, 189.6. Compound **4**: Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.30; H, 7.78; N, 7.23. Mp: 109−111 °C. $[\alpha]^{25}_D$ (*c* 0.88, MeOH) +140.7. IR (CH_2Cl_2) ν (cm^{-1}): 1694, 1639. ESI^+ (*m*/*z*): 387. ^1H NMR ($CDCl_3$) δ: 1.30−1.78 (m, 15H), 2.27−2.48 (m, 1H), 2.74 (dd, 1H, J = 17.1, 7.5 Hz), 3.52−3.80 (m, 1H), 3.83−3.98 (m, 2H), 4.38−4.65 (m, 3H), 5.05 (d, 1H, J = 7.2 Hz), 7.11 (d, 1H, J = 7.2 Hz), 7.21−7.41 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 22.7, 24.0, 27.0, 27.3, 28.4, 36.7, 54.9, 55.9, 56.8, 58.9, 64.6, 80.7, 94.0, 94.8, 97.7, 127.2, 127.6, 129.0, 136.8, 153.0, 154.2, 189.6.

(1*S*,2′*R*)-1-(1′-Benzyl-4′-oxo-1′,2′,3′,4′-tetrahydropyridin-2′-yl)-2-hydroxyethylcarbamic Acid *tert*-Butyl Ester (5). To a solution of compound **4** (500 mg, 1.30 mmol) in THF (30 mL) at 25 °C was added a 4 N aqueous solution of HCl (6 mL). After 2 h of stirring, the solvent and HCl were eliminated under reduced pressure. The white residue was dissolved in a mixture of THF−H_2O 5:1 (36 mL) and treated with $Na_2CO_3 \cdot 10H_2O$ (1.30 g, 4.6 mmol) and $(Boc)_2O$ (0.42 g, 2.0 mmol). After stirring for 12 h at 25 °C, the reaction mixture was washed with brine (10 mL), and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to give a residue, which was purified by a silica gel column chromatography (CH_2Cl_2−MeOH, 9:1), yielding 0.43 g of compound **5** (95%) as an oil. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.73; H, 7.51; N, 8.13. $[\alpha]^{25}_D$ (*c* 0.84, MeOH) +268.1. IR (CH_2Cl_2) ν (cm^{-1}): 3621, 3433, 1707, 1637. ESI^+ (*m*/*z*): 347. ^1H NMR ($CDCl_3$) δ: 1.46 (m, 9H), 2.46 (br d, 1H, J = 17.4 Hz), 2.63−2.76 (m, 1H), 3.69−3.87 (m, 3H), 4.02−4.13 (m, 1H), 4.46 (d, 1H, J = 15.0 Hz), 4.54 (d, 1H, J = 15.0 Hz), 4.98 (d, 1H, J = 7.2 Hz), 5.46 (d, 1H, J = 7.5 Hz), 7.13 (d, 1H, J = 7.2 Hz), 7.25−7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 28.4, 36.3, 51.6, 56.5, 58.9, 61.1, 79.9, 97.2, 127.7, 128.3, 129.1, 136.6, 153.5, 155.8, 190.7.

(1*S*,2′*R*,4′*R*)-1-(1′-Benzyloxycarbonyl-4′-hydroxypiperidin-2′-yl)-2-hydroxyethylcarbamic Acid *tert*-Butyl Ester (6a) and (1*S*,2′*R*,4′*S*)-1-(1′-Benzyloxycarbonyl-4′-hydroxypiperidin-2′-yl)-2-hydroxyethylcarbamic Acid *tert*-Butyl Ester (6b). A solution of alcohol **5** (300 mg, 0.87 mmol) in MeOH (50 mL) was hydrogenated, at atmospheric pressure and at 50 °C, in a suspension of Raney Ni and H_2O 1:1 (10 mL). After stirring for 48 h, the reaction was filtered through Celite, and the solvent was evaporated. The white residue was dissolved in a mixture of THF−H_2O 5:1 (18 mL) and treated with $Na_2CO_3 \cdot 10H_2O$ (324 mg, 1.13 mmol) and CbzCl (193 mg, 1.13 mmol). After stirring for 12 h at 25 °C, the reaction was washed with brine (10 mL), and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and evaporated to give a residue, which was purified by a silica gel column chromatography (CH_2Cl_2−MeOH, 9:1), yielding 302 mg of a white solid corresponding to the mixture of diols **6a** and **6b** (88%) in a ratio of 7:3. This mixture of alcohols was used in the next step without purification. ESI^+ (*m*/*z*): 394 + Na (NMR data, extracted from the mixture **6a**/**6b**, for the major product). ^1H NMR ($CDCl_3$) δ: 1.36 (m, 9H), 1.52−1.84 (m, 3H), 1.94−2.17 (m, 1H), 3.25−3.52 (m, 1H), 3.61−3.80 (m, 2H), 3.82−4.32 (m, 5H), 4.39−4.58 (m, 1H), 5.11 (s, 2H), 5.19−5.35 (m, 1H), 7.34 (br s, 5H). ^{13}C NMR ($CDCl_3$) δ: 28.2, 31.3, 32.0, 34.6, 51.0, 52.9, 63.3, 63.5, 67.2, 79.3, 127.7, 128.0, 128.5, 136.5, 155.9, 156.5.

(2*S*,2′*R*)-*tert*-Butoxycarbonylamino-(4′-oxopiperidin-2′-yl)-acetic Acid (8). To a solution of diols **6a**/**6b** (350 mg, 0.89 mmol) in acetone (15 mL), at 0 °C, was dropwise added (5 min) the Jones reagent (2.22 mmol). After stirring at the same temperature for 3 h, the reaction was allowed to stand at 25 °C for another 3 h. The excess of the Jones reagent was destroyed by treatment with 2-propanol. This mixture was diluted with H_2O and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give 325 mg (90%) of a colorless oil, corresponding to (2*S*,2′*R*)-*tert*-butoxycarbonylamino-(1′-benzyloxycarbonyl-4′-oxopiperidin-2′-yl)-acetic acid **7**, which was used in the next step without purification. $[\alpha]^{25}_D$ (*c* 0.84, MeOH) +16.0. IR (CH_2Cl_2) ν (cm^{-1}): 3425, 1756, 1712. ESI^- (*m*/*z*): 405. ^1H NMR ($CDCl_3$) δ: 1.40 (m, 9H), 2.37−2.51 (m, 2H), 2.52−2.87 (m, 2H), 3.31−3.62 (m, 1H), 4.09−4.54 (m, 2H), 4.75−4.95 (m, 1H), 5.15 (s, 2H), 7.34 (br s, 5H). ^{13}C NMR ($CDCl_3$) δ: 28.2, 39.6, 39.7, 41.8, 53.6, 56.0, 68.1, 80.7, 128.0, 128.3, 128.6, 135.5, 155.7, 156.2, 173.1, 206.6. A solution of compound **7** (230 mg, 0.57 mmol) in MeOH (20 mL) was hydrogenated at atmospheric pressure and at 25 °C, using 10% palladium−charcoal (40 mg). After stirring for 12 h, the reaction mixture was filtered through Celite, and the solvent was evaporated to obtain 152 mg of the β-amino acid **8** (98%), which was used in the next step without purification. $[\alpha]^{25}_D$ (*c* 1.50, MeOH) +15.9. ESI^- (*m*/*z*): 271. ^1H NMR (CD_3OD) δ: 1.46 (m, 9H), 1.55−1.72 (m, 1H), 1.74−1.95 (m, 1H), 2.02−2.35 (m, 2H), 2.95−3.50 (m, 4H), 3.54−3.72 (m, 1H), 4.31−4.43 (m, 1H). ^{13}C NMR (CD_3OD) δ: 31.2, 35.5, 35.9, 38.4, 39.0, 46.3, 46.5, 58.8, 59.4, 84.0, 97.1, 97.5, 160.3, 175.0, 205.3.

(6*R*,7*S*)-7-*tert*-Butoxycarbonylamino-1-azabicyclo[4.2.0]-octa-4,8-dione (1). To a solution of 2-chloro-1-methylpyridinium iodide (250 mg, 0.95 mmol) in acetonitrile (20 mL) was added Et_3N (0.3 mL, 2.2 mmol), and the mixture was warmed to 70 °C. At this temperature, a solution of β-amino acid **8** (70 mg,

0.26 mmol) in acetonitrile (20 mL) was dropwise added. After stirring for 17 h at 25 °C, the mixture reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated to give a residue, which was purified by a silica gel column chromatography (hexane−ethyl acetate, 3:7), yielding 30 mg of a white solid corresponding to carbacepham **1** (45%). Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.63; H, 7.12; N, 11.03. Mp: 196−197 °C. $[\alpha]^{25}_D$ (*c* 0.45, $CHCl_3$) +131.9. IR ($CHCl_3$) ν (cm^{-1}): 3436 (NH), 1759, 1715. ESI^+ (*m*/*z*) 255. ^1H NMR ($CDCl_3$) δ: 1.42 (s, 9H), 2.33−2.63 (m, 4H), 3.12−3.28 (m, 1H), 3.91−4.01 (m, 1H), 4.22 (ddd, 1H, J = 13.5, 7.8, 2.1 Hz), 5.02−5.10 (m, 1H), 5.52 (d, 1H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 28.1, 38.7, 39.9, 40.7, 54.3, 61.8, 80.9, 155.0, 165.8, 205.9.

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Supporting Information Available: A full listing of ^1H and ^{13}C NMR data of all the new compounds with peak assignments, copies of ^1H and ^{13}C NMR spectra and $^1H-^1H$ and $^1H-^{13}C$ correlations for **3**, **4**, **5** and **1**, and the crystal structure data for **4** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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