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Preparation of Tricyclic Nitrogen Heterocycles via Intramolecular Diels-Alder Reaction of Furans

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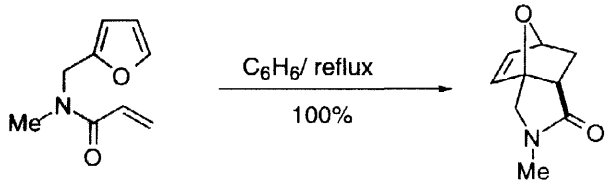
Abstract: Preparation of rigid tricyclic nitrogen heterocycles through acylation of *N*-alkylfurfurylamines with fumaric and maleic acid derivatives has been studied. The reaction proceeds via an initial amide formation followed by an intramolecular Diels-Alder (IMDA) reaction. Various acylation conditions have been studied. Influence of steric and electronic effects on the product formation has also been investigated. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Acylation, Anhydrides, Cycloadditions, Diels-Alder reactions, Dienes, Epoxidation, Furans, Lactams, Substituent effects.

Furans have been used as electron rich diene partners in the Diels-Alder reactions to prepare rigid oxygenated bicyclic systems enroute to various natural products.[2] When a furan is connected to a dienophile by a tether, the triene undergoes intramolecular Diels-Alder (IMDA) reaction with excellent stereocontrol to provide a tricyclic system.[3,4] Since Parker's initial report[4a] on the preparation of tricyclic lactam **2** in quantitative yield by heating triene **1** in benzene, several groups have studied and utilized this reaction (Scheme 1).[4b-j] When an unactivated or monoactivated dienophile is part of the triene, the cycloaddition proceeds at a higher temperature or in the presence of a Lewis acid catalyst. Jung and coworkers have investigated the influence of alkyl substituents on the tether connecting the furan and the dienophile on the rate of IMDA reaction of furfuryl fumarate.[4q-s] Recently, Sandhu et al. have successfully prepared rigid tricyclic compounds in a single step from acylation of *N*-furfurylarylamines with fumaroyl chloride.[4e] The products are formed via an initial amide formation followed by an IMDA reaction. Although this is a simple and efficient route to construct rigid tricyclic molecules, this reaction has not been fully utilized in organic synthesis. As part of our medicinal chemistry program directed toward the identification of novel biologically active molecules, we were interested in investigating the IMDA reaction of furans to prepare substituted rigid tricyclic nitrogen heterocycles.[5] Since a wide range of activated dienophile acids such as fumaric and maleic acid derivatives are commercially available, an efficient mild acylation condition using these acids would greatly increase the synthetic utility of this reaction. Herein we describe our efforts on the preparation of cis and trans tricyclic nitrogen heterocycles through acylation of sterically diverse *N*-benzylfurfurylamines with electronically different dienophile acids.[6]

Scheme 1



1 **2**

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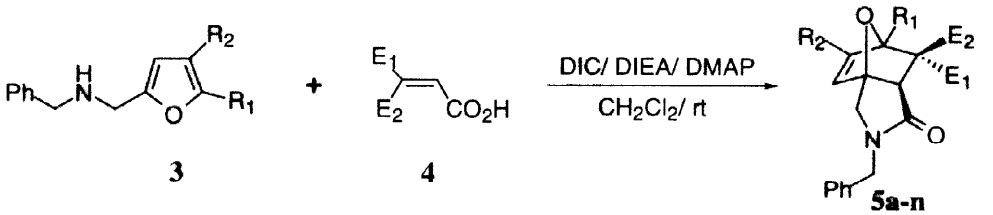
Our acylation study was carried out with *N*-benzylfurfurylamines **3a-c** which were readily prepared in two steps from the corresponding furaldehydes and benzylamine via reductive alkylation procedure.[4d] Initially, **3a** was treated with acid chloride of **4a** (E_1= CO_2Et, E_2= H), prepared using oxalyl chloride, in the presence of diisopropylethylamine (DIEA) and 4-dimethylaminopyridine (DMAP) to yield **5a** in high yield (>80%). The relative trans stereochemistry at C-3 and C-4 of **5a** was assigned based on the vicinal coupling constant of H_3 and H_4 in the ^{1}H NMR spectrum ($J_{3,4}$ = 3.7 Hz).[7] In order to confirm whether **5a** was formed via an initial *N*-acylation followed by an intramolecular Diels-Alder reaction or via an initial intermolecular Diels-Alder reaction followed by *N*-acylation, diene **3a** and dienophile acid **4a** were taken in CH_2Cl_2 and stirred at room temperature. Under this condition, no intermolecular Diels-Alder cycloaddition product formation was observed and only the starting materials were recovered. It was evident from this experiment that initial amide formation was necessary to bring both the diene and the dienophile into the desired conformation to undergo intramolecular cycloaddition.

Acylation of **3a** with acid chloride of maleic acid **4b** (E_1= H, E_2= CO_2Et) furnished an unexpected 90:10 mixture of trans lactam **5a** and cis lactam **5b**. The cis and trans ratio was determined by careful integration of the crude reaction mixture. Presumably, the trans compound **5a** may have formed due to the epimerization at the C-4 stereocenter of **5b** under the acylation condition. In order to synthesize cis lactam **5b** from **4b** in high yield without contamination of any **5a**, alternate acylation conditions were investigated. First, acylation of **3a** with **4b** in the presence of 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (WSC.HCl) and N-hydroxybenzotriazole (HOBt) was examined.[8] Unfortunately, this route also resulted in the isolation of a mixture of **5a** and **5b**. We then turned our attention to acylation of **3a** using symmetrical anhydrides. Although several efficient approaches are readily available to prepare symmetrical anhydrides from the acids, we preferred the 1,3-diisopropylcarbodiimide (DIC) approach.[9] Accordingly, two equivalents of **4b** and one equivalent of DIC were taken in CH_2Cl_2 and stirred at room temperature for 45 minutes to furnish the anhydride. Two different strategies were examined to optimize the acylation condition. In one approach, **3a** was directly added to the anhydride solution and then DIEA and DMAP were added. In a second approach, the insoluble urea was first filtered to provide a clear anhydride solution which was then treated with **3a** in the presence of DIEA and DMAP. To our surprise, irrespective of the approach used, the desired **5b** was isolated as the major product (>95%) in 75% yield (Scheme 2, entry 2). As before, the relative stereochemistry at C-3 and C-4 of **5b** was determined based on the vicinal coupling constant of H_3 and H_4 in the ^{1}H NMR spectrum ($J_{3,4}$ = 9 Hz).[7] Acylation of **3a** with **4a** under this condition provided the trans lactam **5a** in 89% yield (entry 1). Since acylation of **3a** using DIC activation yielded the desired cycloaddition products in high yields, this acylation condition was primarily used as the optimal condition in our studies.

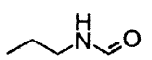
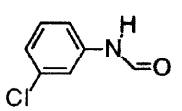
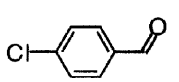
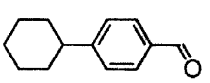
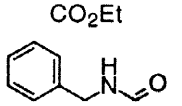
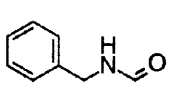
Encouraged by our initial results, and to study the scope of this reaction, diene **3a** was then acylated with different dienophile acids **4c-4g** (entries 3 to 7). To the best of our knowledge, acylation of furans with electronically diverse dienophile acids has not been fully investigated in the preparation of highly functionalized rigid tricyclic nitrogen heterocycles. Acylation of **3a** with alkyl and aryl maleamic anhydrides, prepared from **4c** and **4d**, provided the desired cis lactams **5c** and **5d** in 70% and 74% yields, respectively, after purification (entries 3 and 4). This approach was then extended to acetyl and benzoyl acrylic acids. Acylation of **3a** with acetyl and benzoyl acrylic acids **4e-4g** furnished the corresponding trans lactams **5e-5g** in good yields (entries 5 to 7).

Scheme 2



a. R_1 = H R_2 = H
b. R_1 = Me R_2 = H
c. R_1 = Me R_2 = Me

a. E_1 = CO_2Et E_2 = H
b. E_1 = H E_2 = CO_2Et
c. E_1 = H E_2 = Pr-NH-CO
d. E_1 = H E_2 = 3-Cl-Ph-NH-CO
e. E_1 = CH_3-CO E_2 = H
f. E_1 = 4-Cl-Ph-CO E_2 = H
g. E_1 = 4-Cy-Ph-CO E_2 = H
i. E_1 = H E_2 = Bn-NH-CO

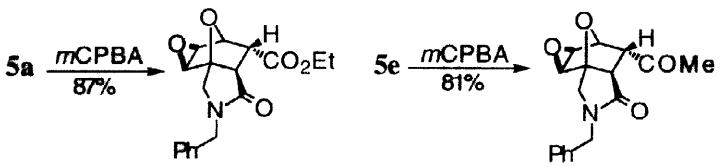
Entry	Compound	R_1	R_2	E_1	E_2	Yield %
1	**5a**	H	H	CO_2Et	H	89
2	**5b**	H	H	H	CO_2Et	75
3	**5c**	H	H	H		70
4	**5d**	H	H	H		74
5	**5e**	H	H	CH_3-CO	H	83
6	**5f**	H	H		H	80
7	**5g**	H	H		H	78
8	**5h**	CH_3	H	CO_2Et	H	79
9	**5i**	CH_3	H	H	CO_2Et	63
10	**5j**	CH_3	H	H		65
11	**5k**	CH_3	H	CH_3-CO	H	80
12	**5l**	CH_3	CH_3	CO_2Et	H	74
13	**5m**	CH_3	CH_3	H	CO_2Et	60
14	**5n**	CH_3	CH_3	H		64

Influence of the steric effects on the cycloaddition process was studied by subjecting furfurylamines **3b** and **3c** to the acylation condition with selected dienophile acids (entries 8 to 14). Irrespective of the substituents on the furan ring, acylation of **3b** and **3c** with **4a**, **4b**, **4e** and **4i** proceeded at room temperature and provided the desired cycloaddition products **5h**-**5n** in moderate to high yields (entries 8 to 14). These results clearly

indicate that the substituents on the furfurylamines **3b** and **3c** do not have any major influence on the cycloaddition process. Both **3b** and **3c** provided highly substituted rigid tricyclic molecules with two quaternary centers. These rigid compounds were stable and did not undergo any retro Diels-Alder reaction even after storing at room temperature for a longer period of time.

Having established an approach to prepare highly functionalized rigid tricyclic molecules in high yields, we then focused our attention on the functionalization of the carbon-carbon double bond of the lactams. In our preliminary study, lactams **5a** and **5e** were treated with 3-chloroperoxybenzoic acid (*m*CPBA) to provide the epoxides **6** and **7** in 87% and 81% yields, respectively (Scheme 3). In the case of lactam **5e**, no Baeyer-Villiger oxidation product was observed. These epoxides could further be transformed to synthetically useful intermediates by opening with various nucleophiles. This approach would increase the utility of this reaction in organic synthesis

Scheme 3



6 **7**

In summary, we have described the preparation of rigid cis and trans tricyclic nitrogen heterocyles under mild conditions through an initial *N*-acylation followed by an intramolecular Diels-Alder reaction. Both steric and electronic effects do not have any major influence on the product formation. Furthermore, functionalization of the carbon-carbon double bond of the lactams has also been investigated. Extension of this methodology to acyclic and pyrrole dienes is currently under investigation and the results will be reported in due course.

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Experimental Section

All the chemicals were purchased from the commercial suppliers (Aldrich, Lancaster, TCI and Nova Biochem) and used without further purification. Infrared spectra were recorded on an FTIR as a liquid film or as a thin crystalline film. ^{1}H NMR spectral data were obtained on a Varian Gemini 400 instrument with the solvents noted. Chemical shifts were reported in the δ scale in ppm relative to TMS (0.00 ppm) as internal standard. ^{13}C NMR spectra were obtained by using the above instrument operating at 100 MHz with solvents noted. Flash column chromatography was carried out using silica gel 60 (230-400 mesh).

General Procedure for the Preparation of Tricyclic Compounds (5): To a solution of dienophile acid (3.70 mmol) in CH_2Cl_2 (6 mL) was added DIC (1.85 mmol) and the mixture was stirred at room temperature for 45 min. The insoluble urea was filtered off and the filtrate was added to a solution of **3** (1.23 mmol) in CH_2Cl_2 (3 mL) and then DIEA (3.70 mmol) and DMAP (catalyst) were added to the reaction mixture. After the furfurylamine was consumed, the reaction mixture was diluted with CH_2Cl_2 and successively washed with saturated aqueous $NaHCO_3$ (1x), 10% aqueous HCl (1x) and saturated aqueous NaCl. The organic layer

was dried, filtered, and evaporated to give the crude compound which was purified by silica gel chromatography (eluted with hexanes/ EtOAc) to provide the desired product.

Compound **5a**. IR (neat) 2980, 1728, 1676, 1468, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$). δ 1.26 (t, J= 7.3 Hz, 3H), 2.97 (d, J = 3.7 Hz, 1H), 3.51 (dd, J = 4.7, 3.7 Hz, 1H), 3.54 (d, J = 12.0 Hz, 1H), 3.86 (d, 12.0 Hz, 1H), 4.14 (qd, 7.3, 1.1 Hz, 2H), 4.45 (d, J = 15.0 Hz, 1H), 4.62 (d, J = 15.0 Hz, 1H), 5.27 (dd, 4.8, 1.7 Hz, 1H), 6.32 (dd, J = 5.9, 1.7 Hz, 1H), 6.51 (d, J = 5.9 Hz, 1H), 7.22-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 23.8, 47.1, 49.2, 51.8, 61.6, 80.8, 90.7, 128.1, 128.3, 129.2, 135.3, 135.5, 136.3, 170.8, 173.0; HRMS (FAB) calcd for $C_{18}H_{19}NO_4$ (M+H) 314.1393, found 314.1390.

Compound **5b**. IR (neat) 3012, 2926, 1726, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, J = 7.0 Hz, 3 H), 2.74 (d, J = 9.4 Hz, 1H), 2.83 (d, J = 9.4 Hz, 1H), 3.65 (d, J = 11.7 Hz, 1H), 3.80 (d, J = 11.7 Hz, 1H), 4.28 (qd, J = 7.0, 2.2 Hz, 2H), 4.38 (d, J = 15.0 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 5.18 (d, J = 1.7 Hz, 1H), 6.43 (dd, J = 5.9, 1.7 Hz, 1H), 6.47 (d, J = 5.9 Hz, 1H), 7.24-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 44.8, 46.4, 47.9, 51.1, 61.0, 81.3, 88.3, 127.3, 127.6, 128.5, 135.1, 135.8, 136.5, 170.3, 171.5; HRMS (FAB) calcd for $C_{18}H_{19}NO_4$ (M+H) 314.1393, found 314.1390.

Compound **5c**. IR (neat) 2961, 2926, 1689, 1666, 1531, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.52 (m, 2H), 2.73 (d, J = 9.0 Hz, 1H), 2.79 (d, J = 9.0, 1H), 3.22 (m, 2 H), 3.66 (d, J = 11.7 Hz, 1H), 3.82 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 14.6 Hz, 1H), 4.54 (d, J = 14.6 Hz, 1H), 5.29 (d, J = 1.8 Hz, 1H), 6.44 (dd, J = 5.9, 1.8 Hz, 1H), 6.47 (d, J = 5.9 Hz, 1H), 6.97 (b, 1H), 7.22 - 7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 22.8, 41.7, 47.0, 47.4, 48.3, 51.0, 82.9, 89.0, 127.8, 128.0, 128.8, 135.3, 135.8, 136.7, 170.4, 170.9; HRMS (FAB) calcd for $C_{19}H_{22}N_2O_3$ (M+H) 327.1710, found 327.1701.

Compound **5d**. IR (neat) 3065, 2999, 1706, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.86 (d, J = 9.3 Hz, 1H), 2.89 (d, J = 9.3 Hz, 1H), 3.68 (d, J = 12.0 Hz, 1H), 3.86 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H), 4.61 (d, J = 14.6 Hz, 1H), 5.40 (s, 1H), 6.48 (m, 2H), 7.04 - 7.60 m, 9H), 9.10 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 48.3, 48.4, 51.3, 82.7, 89.2, 118.4, 120.3, 124.3, 128.0, 128.2, 129.0, 130.0, 134.4, 135.5, 135.6, 136.5, 139.1, 169.1, 171.0; HRMS (FAB) calcd for $C_{22}H_{19}ClN_2O_3$ (M+H) 395.1163, found 395.1168.

Compound **5e**. IR (neat) 3082, 3019, 2996, 1705, 1664, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.89 (d, J = 4.0 Hz, 1H), 3.54 (d, J = 12.1 Hz, 1H), 3.62 (dd, J= 4.4, 4.0 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 15.0 H, 1H), 4.60 (d, J = 15.0 Hz, 1H), 5.26 (dd, J = 4.4, 1.5 Hz, 1H), 6.32 (dd, J = 5.9, 1.5 Hz, 1H), 6.46 (d, J = 5.9 Hz, 1H) 7.22-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.9, 46.9, 49.1, 50.8, 55.7, 80.3, 90.4, 127.7, 127.9, 128.8, 134.6, 134.7, 135.8, 172.6, 204.5; HRMS (FAB) calcd for $C_{17}H_{17}NO_3$ (M+H) 284.1287, found 284.1291.

Compound **5f**. IR (neat) 3089, 3065, 3031, 1682, 1467 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.99 (d, J = 4.0 Hz, 1H), 3.59 (d, J = 12.0 Hz, 1H), 3.87 (d, J = 12.0 Hz, 1H), 4.28 (dd, J = 4.4, 4.0 Hz, 1H), 4.54 (d, J = 15 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 5.32 (dd, J = 4.4, 1.5 Hz, 1H), 6.42 (m, 2H), 7.24 - 7.38 (m, 5H),

7.48 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.0, 49.0, 51.8, 51.9, 81.4, 90.6, 127.8, 127.9, 128.9, 129.1, 130.5, 133.5, 134.3, 135.7, 136.5, 140.1, 172.8, 196.1; HRMS (FAB) calcd for $C_{22}H_{18}ClNO_3$ (M+H) 380.1054, found 380.1053.

Compound **5g**. IR (neat) 3009, 2916, 1698, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 - 1.50 (m, 5H), 1.66 - 1.92 (m, 5H), 2.57 (m, 1H), 3.10 (d, J = 4.0 Hz, 1H), 3.58 (d, J = 11.7 Hz, 1H), 3.86 (d, J = 11.7 Hz, 1H), 4.35 (dd, J = 4.4, 4.0 Hz, 1H), 4.54 (d, J = 15.0 Hz, 1H), 4.64 (d, J = 15.0 Hz, 1H), 5.33 (dd, J = 4.4, 1.6 Hz, 1H), 6.34 (dd, J = 5.8, 1.6 Hz, 1H), 6.44 (d, J = 5.8 Hz, 1H), 7.26 - 7.38 (m, 7H), 8.17 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 27.0, 34.3, 45.0, 47.0, 49.0, 51.6, 81.6, 90.8, 127.3, 127.8, 128.0, 128.9, 129.2, 133.6, 134.0, 135.9, 136.1, 154.4, 173.1, 196.4; HRMS (FAB) calcd for $C_{28}H_{29}NO_3$ (M+H) 428.2226, found 428.2231.

Compound **5h**. IR (neat) 2978, 2939, 1733, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J = 7.0 Hz, 3H), 1.78 (s, 3H), 3.08 (d, J = 3.7 Hz, 1H), 3.15 (d, J = 3.7 Hz, 1H), 3.50 (d, J = 11.7 Hz, 1H), 3.80 (d, J = 11.7 Hz, 1H), 4.15 (m, 2H), 4.32 (d, J = 15.0 Hz, 1H), 4.73 (d, J = 15.0 Hz, 1H), 6.15 (d, J = 5.5 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 7.21 - 7.37 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 18.5, 46.6, 49.0, 51.5, 54.6, 61.0, 89.1, 127.4, 127.7, 128.5, 135.0, 137.7, 137.8, 170.3, 172.3; HRMS (FAB) calcd for $C_{19}H_{21}NO_4$ (M+H) 328.1549, found 328.1547.

Compound **5I**. IR (neat) 2979, 2936, 1733, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.0 Hz, 3 H), 1.67 (s, 3H), 2.76 (d, J = 9.0 Hz, 1H), 2.86 (d, J = 9.0 Hz, 1H), 3.67 (d, J = 11.7 Hz, 1H), 3.74 (d, J = 11.7 Hz, 1H), 4.27 (qd, J = 7.0, 1.8 Hz, 2H), 4.35 (d, J = 15.0, Hz, 1H), 4.73 (d, J = 15.0 Hz, 1H), 6.22 (d, J = 5.6 Hz, 1H), 6.49 (d, J = 5.6 Hz, 1H), 7.26 - 7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 16.0, 46.7, 48.3, 48.6, 54.6, 60.9, 87.8, 89.2, 127.4, 127.8, 128.6, 135.9, 136.3, 139.9, 170.3, 170.8; HRMS (FAB) calcd for $C_{19}H_{21}NO_4$ (M+H) 328.1549, found 328.1550.

Compound **5J**. IR (neat) 3071, 3025, 2932, 1681, 1647, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (s, 3H), 2.77 (d, J = 9.2 Hz, 1H), 2.90 (d, J = 9.2 Hz, 1H), 3.55 (d, J = 11.8 Hz, 1H), 3.70 (d, J = 11.8 Hz, 1H), 4.38 (dd, J = 14.7, 5.12 Hz, 1H), 4.45 (s, 2H), 5.5 (dd, J = 14.7, 5.5 Hz, 1H), 6.17 (d, J = 5.5 Hz, 1H), 6.33 (t, J = 5.1 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 7.08 - 7.14 (m, 2H), 7.21 - 7.29 (m, 3H), 7.30 - 7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 44.0, 46.9, 48.4, 50.1, 55.1, 88.0, 89.8, 127.4, 127.7, 128.1, 128.2, 128.6, 128.8, 135.8, 136.2, 138.2, 139.7, 169.8, 170.6; HRMS (FAB) calcd for $C_{24}H_{24}N_2O_3$ (M+H) 389.1866, found 389.1859.

Compound **5k**. IR (neat) 2912, 1673(br) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.3 (s, 3H), 2.81 (d, J = 4.5 Hz, 1H), 3.27 (d, J = 4.5 Hz, 1H), 3.52 (d, J = 11.7 Hz, 1H), 3.80 (d, J = 11.7 Hz, 1H), 4.34 (d, J = 15.0 Hz, 1H), 4.73 (d, J = 15 Hz, 1H), 6.25 (d, J = 5.5 Hz, 1H), 6.41 (d, J = 5.5 Hz, 1H), 7.22 - 7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.0, 30.5, 47.1, 49.5, 55.2, 60.4, 88.9. 89.0, 127.8, 128.0, 128.9, 134.2, 135.8, 139.1, 172.7, 206.2; HRMS (FAB) calcd for $C_{18}H_{19}NO_3$ (M+H) 298.1444, found 298.1436.

Compound **5l**. IR (neat) 2985, 2939, 1726, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.0 Hz, 3 H), 1.70 (d, J = 1.8 Hz, 3H), 1.72 (s, 3H), 3.13 (s, 2H), 3.45 (d, J = 11.7 Hz, 1H), 3.75 (d, J = 11.7 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 4.30 (d, J = 15.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 6.07 (d, J = 1.73 Hz, 1H), 7.22 - 7.38 (m , 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3, 14.4, 17.1, 46.7, 49.1, 51.3, 54.7, 61.0, 88.1, 90.8, 127.4, 127.7, 128.2, 128.6, 135.8, 146.8, 170.0, 172.8; HRMS (FAB) calcd for $C_{20}H_{23}NO_4$ (M+H) 342.1706, found 342.1706.

Compound **5m**. IR (neat) 2979, 2932, 1719, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.3 Hz, 3H), 1.58 (s, 3H), 1.79 (d, J = 1.8 Hz, 3H), 2.67 (d, J = 8.8 Hz, 1H), 2.87 (d, J = 8.8 Hz, 1H), 3.61 (d, J = 11.7 Hz, 1H), 3.69 (d, J = 11.7 Hz, 1H), 4.26 (m, 2H), 4.32 (d, J = 15.0 Hz, 1H), 4.73 (d, J = 15.0 Hz, 1H), 6.04 (d, J = 1.8 Hz, 1H), 7.24 - 7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 14.3, 23.5, 46.5, 47.7, 48.5, 56.2, 60.8, 87.0, 90.4, 127.3, 127.7, 128.5, 129.4, 135.9, 148.5, 170.4, 171.0; HRMS (FAB) calcd for $C_{20}H_{23}NO_4$ (M+H) 342.1706, found 342.1713.

Compound **5n**. IR (neat) 3065, 3025, 2939, 1680, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.58 (s, 3H), 1.76 (d, J = 1.8 Hz, 3H), 2.68 (d, J = 9.2 Hz, 1H), 2.91 (d, J = 9.2 Hz, 1H), 3.50 (d, J = 11.7 Hz, 1H), 3.65 (d, J = 11.7 Hz, 1H), 4.36 (dd, J = 14.3, 5.1 Hz, 1H), 4.45 (s, 2H), 4.55 (dd, J = 14.3, 5.9 Hz, 1H), 6.02 (b, 1H), 6.32 (b, 1H), 7.09 - 7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.6, 44.0, 46.8, 48.4, 49.7, 56.6, 87.1, 91.1, 127.3, 127.6, 128.0, 128.2, 128.5, 128.8, 129.3, 135.9, 138.1, 148.2, 170.0, 170.9; HRMS (FAB) calcd for $C_{25}H_{26}N_2O_3$ (M+H) 403.2022, found 403.2018.

General Procedure for the Preparation of Epoxides 6 and 7: To a solution of **5a** (0.6 g, 1.92 mmol) in CH_2Cl_2 (30 mL) was added 3-chloroperoxybenzoic acid (3.88 mmol, Aldrich, 57-86%) and the mixture was stirred at room temperature for 12h. The reaction mixture was diluted with CH_2Cl_2 and successively washed with saturated aqueous $NaHCO_3$ (1x) and saturated aqueous NaCl. The organic layer was dried, filtered, and evaporated to give the crude compound which was purified by silica gel chromatography (60:40 to 40:60 hexanes : EtOAc) to provide **6** (0.55 g, 87 % yield).

Compound **6**. IR (neat) 2980, 2921, 1735, 1694, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.0 Hz, 3H), 3.19 (d, J = 4.0 Hz, 1H), 3.45 (d, J = 3.3 Hz, 1H), 3.49-3.51 (m, 2H), 3.54 (d, J = 12.1 Hz, 1H), 3.72 (d, J = 12.1 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.46 (d, J =15.0 Hz, 1H), 4.55 (d, J = 15.0 Hz, 1H), 4.79 (d, J = 5.1 Hz, 1H), 7.2 - 7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 47.0, 47.8, 48.8, 50.8, 52.1, 76.6, 76.7, 86.2, 127.9, 128.0, 128.9, 135.5, 169.5, 171.4; HRMS (FAB) calcd for $C_{18}H_{19}NO_5$ (M+H) 330.1342, found 330.1333.

Compound **7**. IR (neat) 3005, 2906, 1709. 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.06 (d, J = 4.8 Hz, 1H), 3.47 (d, J = 3.3 Hz, 1H), 3.51 (d, J = 3.3 Hz, 1H), 3.55 (d, J = 12.1 Hz, 1H), 3.62 (t, J = 4.8 Hz, 1H), 3.73 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 15.0 Hz, 1H), 4.53 (d, J = 15.0 Hz, 1H), 4.79 (d, J = 4.8 Hz, 1H), 7.21-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 46.9, 47.9, 48.8, 48.9, 50.9, 59.6, 76.5, 85.9, 127.8, 127.9, 128.9, 135.4, 171.6, 204.2; HRMS (FAB) calcd for $C_{17}H_{17}NO_4$ (M+H) 300.1236, found 300.1235.

References and Notes

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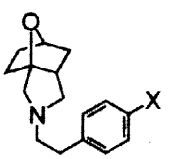
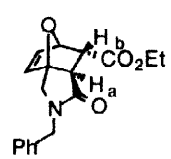
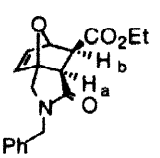
5. Rigid tricyclic nitrogen heterocycles have been shown to have interesting biological properties. For example, Figure 1 has been reported to have antipsychotic and antidyskinetic properties. Source: MDL Drug Data Registry, by MDL information systems, Inc.; San Leandro, California, USA.

Figure 1 X = Cl, F 

6. Presented at the 213th ACS National Meeting, San Francisco, CA; April 1997, ORGN 575.
7.  **5a** trans $J_{a,b}$ = 3.7 Hz  **5b** cis $J_{a,b}$ = 9.4 Hz
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