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Intra-molecular Diels–Alder reactions of citraconamic acids from furfurylamines and citraconic anhydride: effects of substitution in the furan ring on regioselectivity

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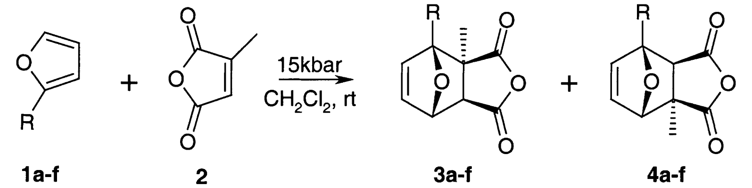
Abstract—Regioselectivity in the intra-molecular Diels–Alder (IMDA) reaction of furfurylcitraconamic acids derived from *N*-benzylfurfurylamines and citraconic anhydride can be controlled by substituents located in the furan ring and by reaction conditions. Reactions conducted under kinetic conditions resulted in cycloaddition products having methyl and aminomethylene substituent in 1,3-relationship whereas under thermodynamic conditions, excepting in the case of the 3-methylsulfanyl group, the products rearranged to more stable cycloadducts in which the substituents are in 1,2-relationship. Product formation can be explained on the basis of frontier orbital interactions and steric considerations. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The intra-molecular Diels–Alder (IMDA) reaction of furans with built-in dienophiles is an effective method for the generation of highly functionalized polycyclic systems, which are attractive precursors for natural product synthesis.[1,2] IMDA reactions between unactivated furans and dienophiles take place generally at lower temperature compared to their inter-molecular counterparts,[3,4] and thus, they have a much higher scope with respect to the necessary activation of the reaction partners.[5] Furthermore, success of IMDA cycloaddition critically depends on the length of the tether connecting the furan with the dienophile unit.[6–8]

We were interested in the cycloaddition reactions of furans with citraconic anhydride as key steps in the synthesis of CD-ring precursors of paclitaxel as well as new derivatives of palasonin.[9] In this context, we found that high pressure mediated cycloadditions of furan **1a** and citraconic anhydride **2** afforded *exo*-adduct **3a** and 2-substituted furans **1b–f** afforded approximate 1:1 mixtures of *exo*regioisomers **3b–f** and **4b–f** (Scheme 1). It occurred to us that regioselectivity in these types of reactions could be controlled using an IMDA cycloaddition. We reasoned that furfurylamines might open citraconic anhydride regioselectively and when followed by IMDA cycloaddition it could lead regioselectively to a cycloadduct. Furfurylamine derivatives were already shown to be attractive substrates for IMDA



1a, 3a, 4a: R = H; **1b,3b,4b**: R = Me; **1c, 3c, 4c**: R = COOEt; **1d, 3d, 4d**: R = $CH_2OCOC(CH_3)_3$; **1e, 3e, 4e**: R = CH_2OAc; **1f, 3f, 4f**: R = CH_2OCH_2Ph.

Scheme 1.

Keywords: IMDA reaction; furfurylamine; citraconic anhydride; citraconamic acid; substituent effects.

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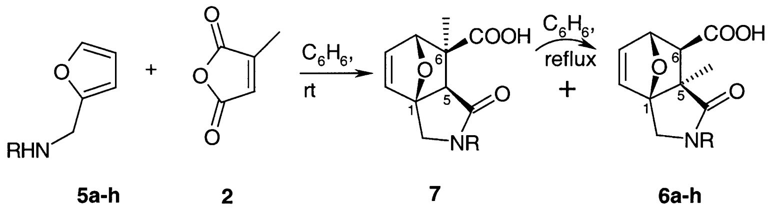


5a, 7, 6a: R = benzyl; **5b, 6b**: R = 2-methylbenzyl; **5c, 6c**: R = 2-hydroxybenzyl; **5d, 6d**: R = 2-methoxybenzyl; **5e, 6e**: R = 4-methoxybenzyl; **5f, 6f**: R = 4-nitrobenzyl; **5g, 6g**: R = 2-naphthylmethyl; **5h, 6h**: R = cyclohexyl.

Scheme 2.

reactions to generate functionalized tetrahydroisoindoline derivatives.[10–14] Bulky groups such as trityl on nitrogen in furfurylamine were found to accelerate the cycloaddition process.[15]

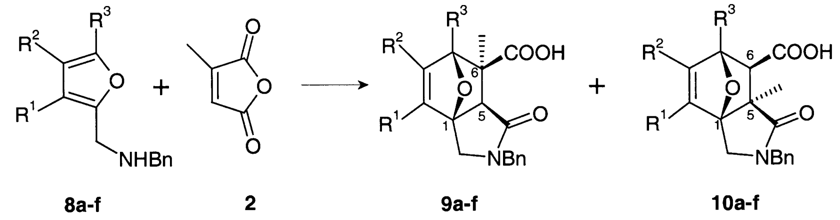
In a preliminary communication we have described results from the reaction of *N*-benzyl furfurylamine **5a** with citraconic anhydride **2** in benzene under reflux which furnished regio and stereochemically pure tricyclic cycloadduct **6a** wherein the C_5–Me and C_1-substitutents were in a 1,2-relationship (Scheme 2, entry 1, Table 1).[16] However, when this reaction was conducted at room temperature, regioisomer **7** was the major product and it rearranged to **6a** on warming. It was also found that substituents on the benzyl group did not exert much influence on the regio- and stereochemical outcome. In all cases reaction of furfurylamines **5b**–**h** with **2** in benzene reflux furnished cycloadducts **6b**–**h** having C_5–Me and C_1-substitutents in a 1,2-relationship.

Above results were intriguing since the 'more crowded' cycloadducts **6a**–**h** were exclusively formed at elevated temperatures. We reasoned that electron donating and withdrawing substituents on the furan ring might have a directing effect on the course of the reaction. In this paper, we describe the results from the reaction of substituted furfurylamines **8a**–**f** with citraconic anhydride **2** (Scheme 3).

2. Results

Variously substituted furfurylamines **8a**–**f** having electron donating substituents such as methylsulfanyl and methyl groups as well as electron withdrawing ester groups, strategically placed on the furan ring, were subjected to reaction with citraconic anhydride **2** in benzene at room temperature and at elevated temperatures (Scheme 3). Ratio of the products formed in the reaction was calculated on the basis of integration of diagnostic signals in the NMR spectra. Results from this study are gathered in Table 1.

Reaction of citraconic anhydride **2** with furfurylamine **8a**, having strongly electron donating 3-methylsulfanyl group proceeded to furnish a single cycloadduct **9a** at rt (entry 2, Table 1). Regio and *exo*-stereochemistry for the adduct **9a**



Scheme 3.

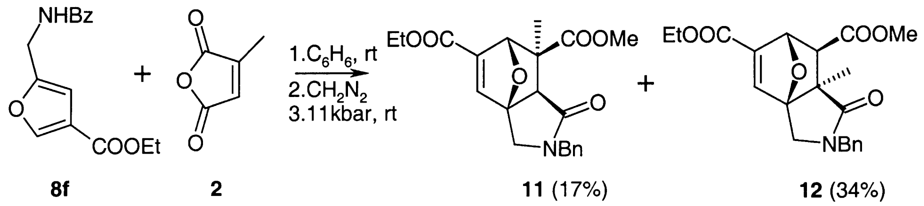
Table 1. Reaction of furfurylamines with citraconic anhydride

Entry	Furfurylamine	Ratio of cycloadducts at rt (24 h)	Ratio of cycloadducts at 65°C (24 h)	Major cycloadduct and yield at 65°C (24 h, %)
1	**5a**	**7/6a**; 65:35	**7/6a**; 5:95	**6a** (90)
2	**8a**	**9a/10a**;100:0	**9a/10a**;100:0	**9a** (80)
3	**8b**	**9b/10b**; 25:75	**9b/10b**; 0:100	**10b** (92)
4	**8c**	**9c/10c**; 85:15	**9c/10c**;15:85	**10c** (82)
5	**8d**	**9d/10d**; 0:100	**9d/10d**; 0:100	**10d** (92)
6	**8e**	–[a]	**9e/10e**; 10:90	**10e** (72)
7	**8f**	–[b]	**9f/10f**; 25:75	**10f** (–[c])

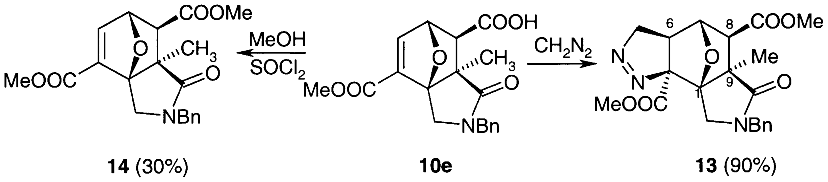
[a] Only 20% conversion to cycloadducts, ratio of cycloadducts **9e/10e**=75:25.

[b] Only 5% conversion to cycloadducts; ratio of cycloadducts **9f/10f**=45:55.

[c] Product was a mixture of regioisomeric cycloadducts and citraconamic acids.



Scheme 4.

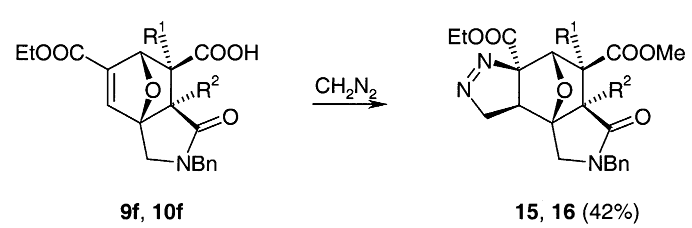


Scheme 5.

was assigned on the basis of 2D NMR NOESY which revealed stereochemical proximity between C_6–methyl hydrogens and C_5–H, C_7–H, C_8–H. ^{1}H NMR spectrum of this adduct showed the C_6–Me hydrogen absorption at 1.33 ppm which is about 0.1 ppm down-field compared to C_5–methyl hydrogen absorption in 1,2-cycloadducts **6a** and **10b–f**. Similarly, ^{13}C NMR spectrum of **9a** showed C_6–methyl carbon absorption at 24.05 ppm; about 2 ppm down-field compared to 1,2-cycloadducts **6a** and **10b–f**. Unlike in the case of the cycloadduct **7** derived from unsubstituted furfurylamine **5a**, the cycloadduct **9a** did not rearrange to its isomer **10a** even in benzene reflux. Reaction of furfurylamine **9b**, having a 4-methylsulfanyl group, with **2** furnished a mixture of cycloadducts **9b**, **10b** at room temperature in the ratio of 25:75 (entry 3). The mixture on warming to 65°C was transformed completely to the thermodynamically stable adduct **10b**. The ^{1}H NMR spectrum of **10b** revealed C_5–Me hydrogen absorption at 1.21 ppm and the ^{13}C NMR spectrum showed C_5–Me carbon absorption at 21.92 ppm; similar to NMR absorptions found in the case of cycloadduct **6a**.[8] Regioselectivity in the IMDA reactions involving other substrates were also noted on the basis of the diagnostic NMR absorption of C–Me groups. In all the cases studied, prolonged reflux (2 days) in benzene or toluene resulted in a complex mixture of products.

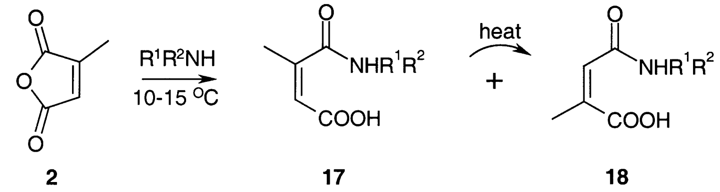
Reaction of 3-methylfurfurylamine **8c** with **2** yielded a mixture of cycloadducts **9c** and **10c** at room temperature in the ratio of 85:15 and the mixture reorganized to 13:87 on warming to 65°C (entry 4). The major product **10c** crystallized out on standing. Reaction of 5-methylfurfurylamine **8d** with **2** resulted in single adduct **10d** at room temperature as well as at 65°C (entry 5).

Reaction of 3-methoxycarbonylfurfurylamine **8e** with **2** produced within 5 min at rt a mixture of citraconamic acids. However, subsequent IMDA reaction was slow and the transformation to cycloadducts after staying at rt for 24 h was only about 20% with the ratio of adducts **9e** and **10e** being 75:25 (entry 6). On warming to 65°C for 24 h the mixture was transformed to cycloadducts **9e** and **10e** in the ratio of 8:92. The major isomer **10e** crystallized out of the reaction mixture on cooling to 5°C. The reaction of



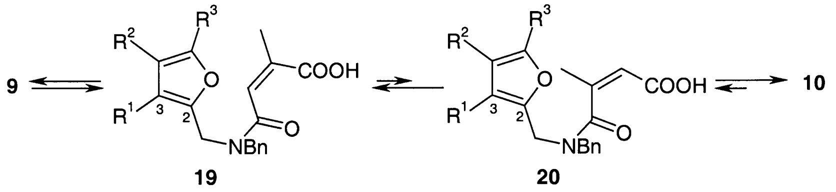
9f, 15: R^1 = Me, R^2 = H; **10f, 16**: R^1 = H, R^2 = Me

Scheme 6.



R^1, R^2 = alkyl, cycloalkyl.

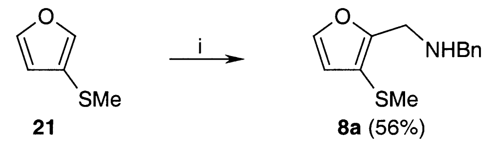
Scheme 7.



Scheme 8.

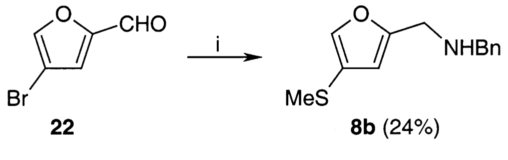
4-ethoxycarbonylfurfurylamine **8f** with **2** also generated a mixture of citraconamic acids at room temperature within 5 min, but the IMDA reaction was very slow, with 5% conversion in 24 h (entry 7). Even after standing for 20 days the conversion of citraconamic acids to IMDA cycloadducts was only 65%. On heating in benzene at 65°C for 24 h IMDA conversion was 92% and the ratio of adducts **9f** and **10f** was 25:75. However, the major cycloadduct **10f** did not crystallize out of the reaction mixture on standing and chromatographic purification of the acids was difficult. Therefore, the adducts were characterized as their methyl esters **11**, **12** generated from IMDA conversion of the mixture of corresponding citraconamic esters under high-pressure conditions (Scheme 4). The diesters **11** and **12** were separated and characterized. Ester **11** was stable at room temperature but equilibrated with its retro IMDA product on warming to 65°C in the NMR tube. The ratio of the corresponding citraconamic ester to that of cycloadduct **11** was 67:33. The ^{1}H NMR spectrum of the mixture revealed two sets of olefinic signals for precursor citraconamic esters indicating the presence of rotomers from amide bond. On subjecting the mixture to high pressure conditions again, the cycloadduct **11** was regenerated. On the other hand, cycloadduct-diester **12** was stable at 65°C and did not equilibrate to the corresponding citraconamic ester.

Attempted esterification of acid-ester **10e** with etherial solution of diazomethane resulted in esterification and concomitant regio- and *exo*-stereochemically selective 1,3-dipolar cycloaddition to generate heterocycle **13** in quantitative yield (Scheme 5). The 2D NOESY spectrum of **13** showed steric proximity of C_8–H with C_9–Me, C_7–H and C_6–H. The desired diester **14** was obtained through esterification with methanol in the presence of thionyl chloride.



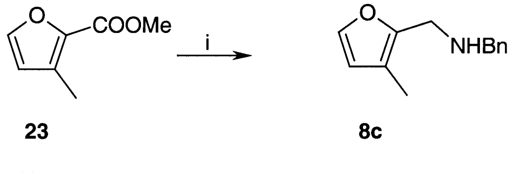
21 **8a** (56%)

Scheme 9. *Reagents and conditions*: (i) (a) LDA, DMF, THF, −78°C; (b) $BnNH_2$, EtOH; (c) $NaBH_4$, EtOH (56% overall).



22 **8b** (24%)

Scheme 10. *Reagents and conditions*: (i) (a) $(EtO)_3CH$, PPTS, EtOH; (b) LDA, MeSSMe, THF, −78°C; (c) H_3O^+; (d) $BnNH_2$, EtOH; (e) $NaBH_4$, EtOH (24% overall).



23 **8c**

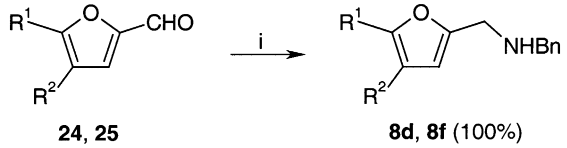
Scheme 11. *Reagents and conditions*: (i) (a) $BnNH_2$, Cat. KCN, MeOH, 10 kbar; (b) LAH, THF (74% overall).

Reaction of the mixture of acids **9f** and **10f** with diazomethane also resulted in 1,3-dipolar addition products **15** and **16** out of which the major isomer **16** was isolated and characterized (Scheme 6).

3. Discussion

Our results show that the stereochemical outcome of the IMDA reactions of furfurylcitraconamic acids is not effected by the regioselectivity in the preceding reaction of furfurylamines with citraconic anhydride. Previously Boyd and co-workers studied the reaction of citraconic anhydride **2** with several primary and secondary amines (Scheme 7).[17] They found that the reaction at 10–15°C furnished citraconamic acids **17** and **18** in which the former isomer predominated. On attempted recrystallisation major isomer **17** rearranged exclusively to **18**. Interestingly, in this case, the final product contained the methyl group next to the carboxylic acid end. This is in contrast to our observations on IMDA reactions with furfurylamine **5a**, where the thermodynamically more stable product **6a** had the methyl group next to the amide carbonyl (Scheme 2). To gain insights about the rearrangement process, the reactions of furfurylamines **5a**, **8a–f** with citraconic anhydride **2** were monitored by ^{1}H NMR spectroscopy. The characteristic methyl signals for cycloadducts occurring at about δ 1.3 ppm (methyl group of **7**, **9a–f**) and at about δ 1.2 ppm (methyl group of **6a**, **10a–f**) were monitored periodically. Observations made in each case lead to the following conclusions: Anhydride ring opening of **2** by the secondary furfurylamines **5a**, **8a–f** took place rapidly within 15 min, leading to a mixture of citraconamic acids as noticed by the appearance of two sets of olefinic proton signals around δ 5.8 and 6.3 ppm. Subsequent IMDA reactions in the case of electron rich furfurylamines **8a–d** was also rapid but they were slow with electron poor furfurylamines **8e–f** (Table 1).

The results show that furans having a substituent at the C_3 position (R^1) react with the dienophile component at rt, 24 h (kinetic circumstances) mainly to cycloadducts of type **9** (entry 2, 4 and 6, Table 1). The selective formation of adducts **9** at rt in these cases is in accordance with predictions based on FMO theory.[18] For all R^1 substituents of **19** the highest HOMO coefficients are expected to be at C_2 of



24, 25 **8d, 8f** (100%)

8d, 24: R^1 = Me, R^2 = H; 8f, 25 = R^1 = H, R^2 = COOEt.

Scheme 12. *Reagents and conditions*: (i) (a) $BnNH_2$, EtOH, rt; (b) $NaBH_4$, EtOH, rt.

the furanyl group (Scheme 8). In the more polarized dienophile having a methyl group next to the carboxylic acid (**19**) the highest LUMO coefficient is expected to be at the less substituted ethene carbon. Cycloaddition via this citraconamic acid intermediate results in kinetically favoured cycloadducts of the type **9**. Based on similar arguments it could be expected that R^2 substituents at C_4 position generate cycloadducts of type **10** as major products under kinetic conditions. Polarization of the dienophile part in **20** is however smaller than in **19**. In the case of **8d**, the electronic effect of the substituent R^3 is marginal as it is counterbalanced by the effect of the aminomethyl substituent at C-1. The selective formation of **10d** also under kinetic circumstances points to a steric effect of this substituent. The low reactivity of furans having alkoxycarbonyl substituent towards IMDA reaction can also be explained on the basis of FMO theory. The alkoxycarbonyl functionality is expected to lower the HOMO energy of the furan moiety resulting in a higher HOMO-LUMO energy gap, thus, leading to a drop in IMDA reactivity. It has been shown that the alkoxycarbonyl group at C-2 of a diene activates the diene in a Diels–Alder reaction with an electron-poor dienophile[19,20] which seems to be in contrast with expectations from FMO theory. This activation has been explained by taking into account the paralocalisation energy of the diene in the transition state. Apparently the effect of the alkoxycarbonyl group in furan is different from that in open dienes and in accordance with FMO theory.

At elevated temperatures, excepting in the case of strongly electron donating methylsulfanyl group in C_3-position, adducts rearrange via citraconamic acid **20** to generate adducts of type **10** almost exclusively. The outcome of cycloadducts **10** as the thermodynamically more stable products in nearly all cases seems at first sight surprising. However, molecular mechanics calculations (MMX mode) indicate that the adducts of the type **10** are more stable than their regioisomers by about 2 Kcal/mol.[21] Thermodynamic stability of the adducts **6a**, **10**, may arise from molecular distortions due to C_5–Me, leading to better hydrogen bonding interactions between the carboxylic acid and the amide carbonyl.

4. Synthesis of furfurylamines

Starting furfurylamines **8a–f**, utilized in this study, were synthesized by reductive amination of the corresponding aldehydes with benzylamine, reduction of the corresponding amide or by displacement of a halogen with benzylamine as described in the following.

The regiospecifically generated carbanion from 3-methylsulfanylfuran[22,23] **21** was formylated with DMF to furnish 3-methylsulfanyl-2-furaldehyde which was reductively aminated with benzylamine to furnish furfurylamine **8a** in 56% overall yield (Scheme 9).

4-Bromo-2-furaldehyde[24] **22** was utilized as a starting material for the synthesis of 4-methylsulfanylfurfurylamine derivative **8b** (Scheme 10). After protection of the aldehyde functionality as diethylacetal, bromine was replaced by a methylsulfanyl group by reaction with LDA and dimethyldisulfide. The intermediate 4-methylsulfanyl-2-furaldehyde, generated after hydrolysis of the acetal, was transformed into furfurylamine **8b** through reductive amination with benzylamine in 24% overall yield.

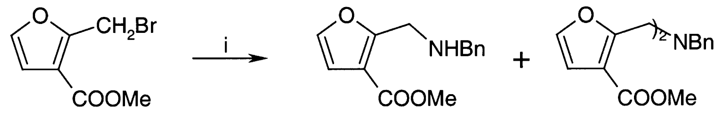
Commercially available methyl 3-methyl-2-furoate **23** served as starting material for the synthesis of 3-methylfurfurylamine derivative **8c** (Scheme 11). The ester functionality in **23** was converted to an amide on reaction with benzylamine in the presence of a catalytic amount of potassium cyanide under high-pressure conditions. Subsequent reduction of the amide with lithium aluminium hydride resulted in furfurylamine **8c** in 74% overall yield.

Secondary furfurylamines **8d** and **8f** were synthesised from the corresponding known aldehydes **24**[25] and **25**[26] by reductive amination with benzylamine in quantitative yields (Scheme 12).

Reaction of bromide **26**[27] with benzylamine furnished a mixture of secondary and tertiary furfurylamines **8e** and **27** which were separated by chromatographic techniques (Scheme 13).

5. Conclusions

In this study we have shown that regioselectivity in the IMDA reaction involving furfurylamines and citraconic



26 **8e** (17%) **27** (34%)

Scheme 13. *Reagents and conditions*: (i) (a) $BnNH_2$, DMF, rt.

anhydride can be controlled by substituents in the furan part and by the reaction circumstances.

6. Experimental

6.1. General remarks

^{1}H NMR, ^{13}C NMR and DEPT spectra were recorded using a Bruker AM-300 (300 and 75 MHz) spectrometer as $CDCl_3$ solutions. 2D NOESY spectra were recorded on Bruker AM-400 (400 MHz) spectrometer. Chemical shift values are reported as δ values in parts per million (ppm) relative to tetramethylsilane as an internal standard. Mass spectra were determined using a double focussing VG 7070E spectrometer. Elemental analysis was performed in triplicate on a Carlo Erba Instruments CHNSO EA 1108 elemental analyser. Melting points were measured on a Reichert Thermopan microscope and are uncorrected. All reactions were monitored for completion by thin-layer chromatography (TLC), which was performed using glass-baked silica gel ($60F_{254}$) plates and the spots were detected with UV light, iodine vapour or basic potassium permanganate solution. Column chromatography was performed using Baker silica gel (70–230 mesh) with heptane/ethyl acetate solvent mixtures. Starting furfurylamines were purified by either distillation under reduced pressure (mmHg) as mentioned in the data or by column chromatography. All the solvents were distilled prior to use. The high pressure apparatus used has been described before.[28] Reactions were carried in sealed 2.5 ml Teflon vessels. Maleic anhydride, furan, 2-furaldehyde, furfurylamine (2-furylmethanamine), methyl 2-methyl-3-furoate, ethyl 3-furoate, 5-methyl-2-furaldehyde and methyl 2-methyl-2-furoate were purchased from commercial sources.

6.2. Representative procedure for the preparation of benzylic amines from furfurylamine and aldehyde

The benzylic amines **5a**–**h** and **8a**–**e** were without further purification used in the next step.

6.2.1. *N*-benzyl-*N*-(2-furylmethyl)amine (5a). Furfurylamine (9.7 g, 0.1 mol) was added to a stirred solution of benzaldehyde (11.14 g, 0.105 mol) in anhydrous ethanol (100 ml) at rt. After complete formation of the imine (45 min, TLC), excess sodium borohydride (7.56 g, 0.2 mol, 2 equiv.) was added in three portions at 10°C. After complete addition, the reaction mixture was stirred for 3 h at rt, and then diluted with water (200 ml), acidified with aq. HCl to pH 1 and extracted with dichloromethane (50 ml×3). The aqueous layer was adjusted to pH 10 with aq. NaOH (2N) and after that extracted with dichloromethane (3×100 ml). The combined dichloromethane layer was washed with brine (2×25 ml), dried ($MgSO_4$) and concentrated in vacuo. Distillation of the crude product under reduced pressure (114–116°C, 1 mm) furnished 16.3 g (87%) of *N*-benzyl-*N*-(2-furylmethyl)amine as an oil; ^{1}H NMR: δ 7.37–7.24 (m, 6H), 6.29–6.34 (m, 1H), 6.16–6.19 (br d, J=3.0 Hz, 1H), 3.78 (s, 4H), 1.69 (br s, 1H); ^{13}C NMR: 153.66, 141.54, 139.71, 128.27, 128.16, 126.77, 109.90, 106.78, 52.51, 45.09 ppm.

6.2.2. *N*-(2-Furylmethyl)-*N*-(2-methylbenzyl)amine (5b). Oil, yield=92% ^{1}H NMR: δ 7.37 (s, 1H), 7.30–7.27 (m, 1H), 7.18–7.15 (m, 3H), 6.32 (dd, J=3.0, 2.0 Hz, 1H), 6.19 (d, J=3.1 Hz, 1H), 3.82 (s, 2H), 3.76 (s, 2H), 2.31 (s, 3H), 1.56 (br s, 1H); ^{13}C NMR: 153.95, 141.74, 137.81, 136.36, 130.24, 128.49, 127.01,.125.85, 110.10, 106.96, 50.40, 45.71, 18.81 ppm.

6.2.3. 2-[(2-Furylmethyl)amino]methylphenol (5c). Oil, yield=92%; ^{1}H NMR: δ 7.39 (d, J=1.5 Hz, 1H), 7.17 (td, J=7.5,1.5 Hz, 1H), 6.96 (d, J=7.5 Hz, 1H), 6.84 (d, J= 7.5 Hz, 1H), 6.77 (td, J=7.5,1.5 Hz, 1H), 6.33 (dd, J=3.1, 1.5 Hz, 1H), 6.19 (d, J=3.0 Hz, 1H), 3.95 (s, 2H), 3.81 (s, 2H); ^{13}C NMR: 158.10, 151.89, 142.19, 128.69, 128.53, 122.0, 118.99, 116.29, 110.18, 107.89, 51.05, 44.10 ppm.

6.2.4. *N*-(2-Furylmethyl)-*N*-(2-methoxybenzyl)amine (5d). Oil, yield=63%; bp: 148–151°C (1 mm); ^{1}H NMR: δ 7.35 (d, J=1.6 Hz, 1H), 7.28–7.18 (m, 2H), 6.95–6.84 (m, 2H), 6.30 (dd, J=3.0, 1.6 Hz, 1H), 6.18 (d, J=3.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 2H), 3.76 (s, 2H), 1.91 (br s, 1H); ^{13}C NMR: 157.60, 154.10, 141.56, 129.87, 128.18, 127.92, 120.27, 110.14, 109.98, 106.64, 55.11, 48.37, 45.42 ppm.

6.2.5. *N*-(2-Furylmethyl)-*N*-(4-methoxybenzyl)amine (5e). Oil, yield=93%; bp: 156–157°C (1 mm); ^{1}H NMR: δ 7.36 (d, J=1.7 Hz, 1H), 7.24 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 6.30 (dd, J=3.0, 1.7 Hz, 1H), 6.17 (d, J=3.0 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 2H), 3.71 (s, 2H), 1.70 (br s, 1H); ^{13}C NMR: 158.77, 153.96, 141.85, 132.07, 129.52, 113.87, 110.16, 107.04, 55.32, 52.26, 45.31 ppm.

6.2.6. *N*-(2-Furylmethyl)-*N*-(4-nitrobenzyl)amine (5f). Oil, yield=56%; ^{1}H NMR: δ 8.17 (d, J=8.6 Hz, 2H), 7.51 (d, J=8.6 Hz, 2H), 7.38 (d, J=1.7 Hz, 1H), 6.32 (dd, J=3.0, 1.7 Hz, 1H), 6.19 (d, J=3.0 Hz, 1H) 3.88 (s, 2H), 3.79 (s, 2H), 1.71 (br s, 1H).

6.2.7. *N*-(2-Furylmethyl)-*N*-(2-naphthylmethyl)amine (5g). Oil, yield=92%; ^{1}H NMR: δ 7.82–7.79 (m, 3H), 7.75 (s, 1H), 7.47–7.37 (m, 4H), 6.32 (dd, J=3.0, 2.0 Hz, 1H), 6.19 (d, J=3.0 Hz, 1H), 3.94 (s, 2H), 3.81 (s, 2H), 1.78 (s, 1H); ^{13}C NMR: 153.88, 141.93, 137.43, 133.48, 132.75, 128.16, 127.71, 126.69, 126.06, 125.64, 110.18, 107.16, 52.94, 45.43 ppm.

6.3. Representative procedure for the preparation of benzylic amines from a furaldehyde and an amine

6.3.1. *N*-benzyl-*N*-(2-furylmethyl)amine (5a). To a stirred solution of the furaldehyde (1 g, 10.5 mmol.) in ethanol (25 ml) was added benzylamine (1.07 g, 10 mmol) at rt. After stirring for 1 h, excess sodium borohydride was added (0.76 g, 20 mmol, 2 equiv.) and stirring continued overnight. Work-up and distillation as described previously furfurylamine was obtained in 83% yield.

6.3.2. *N*-Cyclohexyl-*N*-(2-furylmethyl)amine (5h). Yield= 70%; bp: 82–84°C (1 mm); ^{1}H NMR: δ 7.34 (d, J= 1.7 Hz,1H), 6.30 (dd, J=3.0,1.7 Hz,1H), 6.15 (d, J= 3.0 Hz, 1H), 3.80 (s, 2H), 2.44 (m, 1H), 1.9 (m, 2H), 1.7 (m, 4H),1.2 (m, 5H); ^{13}C NMR: 154.04, 141.12, 109.64, 106.0, 55.35, 42.96, 32.95, 25.78, 24.55 ppm.

6.3.3. *N*-Benzyl-*N*-[3-(methylsulfanyl)-2-furyl]methylamine (8a). Oil, Yield=79%; ^{1}H NMR: δ 7.36–7.25 (m, 6H), 6.40 (d, J=1.9 Hz, 1H), 3.88 (s, 2H), 3.76 (s, 2H), 2.29 (s, 3H), 1.70 (br s, 1H); ^{13}C NMR: 153.89, 141.77, 139.94, 128.36, 128.20, 126.98, 114.82, 113.65, 52.87, 43.41, 19.34 ppm.

6.3.4. *N*-Benzyl-*N*-[4-(methylsulfanyl)-2-furyl]methylamine (8b). Oil, yield=70%; ^{1}H NMR: δ 7.32–7.24 (m, 6H), 6.21 (s, 1H), 3.78 (s, 2H), 3.74 (s, 2H), 2.34 (s, 3H), 1.73 (br s, 1H); ^{13}C NMR: 155.02, 140.41, 139.78, 128.49, 128.28, 127.14, 119.27, 109.81, 52.88, 45.46, 18.43 ppm.

6.3.5. *N*-Benzyl-*N*-[(5-methyl-2-furyl)methyl]amine (8d). Oil, Yield=85%; bp: 119–21°C (0.5 mm); ^{1}H NMR: δ 7.33–7.24 (m, 5H), 6.04 (d, J=2.8 Hz, 1H), 5.88 (d, J=2.8 Hz, 1H), 3.79 (s, 2H), 3.72 (s, 2H), 2.27 (s, 3H), 1.70 (br s, 1H); ^{13}C NMR: 151.94, 151.51, 140.05, 128.44, 128.31, 127.02, 107.92, 105.94, 52.84, 45.46, 13.65 ppm.

6.3.6. Ethyl 5-[(benzylamino)methyl]-3-furoate (8f). Ethyl 3-furoate was formylated to a mixture of ethyl 5-formyl-3-furoate and ethyl 2-formyl-3-furoate in the ratio of 85:15 according to literature procedure,[25] from which the former could be purified by column chromatography. When the mixture was subjected to reductive amination according to the general procedure described previously with benzylamine the corresponding furfurylamines were formed in 88% yield. Isomeric furfurylamine esters were separated by column chromatography. Ethyl 5-formyl-3-furoate (**25**): oil, yield=45%; ^{1}H NMR: 9.69 (s, 1H), 8.21 (s, 1H), 7.28 (s, 1H), 4.35 (q, J=7.1 Hz, 2H), 1.37 (t, J=7.1 Hz, 3H); ^{13}C NMR: 212.0, 177.83, 161.63, 151.43, 121.91, 119.77, 61.20, 14.23 ppm.

6.3.7. Ethyl 5-[(benzylamino)methyl]-3-furoate (8f). Oil, yield=75%; ^{1}H NMR: 7.9 (s, 1H), 7.2–7.4 (m, 5H), 6.54 (s, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.77 (s, 4H), 1.33 (t, J=7.1 Hz, 3H); ^{13}C NMR: 163.17, 155.20, 146.89, 139.53, 128.41, 128.16, 127.08, 119.94, 107.16, 60.34, 52.63, 45.03, 14.25 ppm HRMS calcd for $C_{15}H_{17}NO_3$: 259.12084. Found: 259.12019.

6.3.8. Ethyl 2-[(benzylamino)methyl]-3-furoate. Yield=13%; ^{1}H NMR: 7.2–7.4 (m, 6H), 6.68 (d, J=1 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 4.10 (s, 2H), 3.76 (s, 2H), 2.0 (br s, 1H), 1.31 (t, J=7.2 Hz, 3H); ^{13}C NMR: 163.75, 160.48, 141.26, 139.86, 128.45, 128.26, 127.09, 115.11, 110.93, 60.48, 53.06, 44.80, 14.35 ppm HRMS calcd for $C_{15}H_{17}NO_3$: 259.12084. Found: 259.12072.

6.3.9. *N*-Benzyl-*N*-[(3-methyl-2-furyl)methyl]amine (8c). To a solution of methyl 3-methyl-2-furoate (**23**) (560 mg, 4 mmol) and benzylamine (428 mg, 4 mmol) in methanol (15 ml) in a Teflon tube, was added 30 mg of KCN. The tube was closed and compressed to 10 kbar pressure at room temperature for 16 h after releasing the pressure, the solution was concentrated in vacuo and the resulting viscous liquid was triturated with ether to furnish *N*-benzyl-3-methyl-2-furamide. The amide was recrystallized from ethyl acetate and heptane to yield 671 mg (78%) of the product, mp:96–97°C; ^{1}H NMR: δ 7.35–7.25 (m, 6H), 6.61 (br s, 1H), 6.63 (d, J=1.7 Hz, 1H), 4.59 (d, J=5.9 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR: 159.56, 142.26, 138.39, 128.75, 127.88, 127.74, 127.53, 115.48, 42.83, 11.16 ppm. To a stirred and cooled (0–5°C) suspension of excess LAH (190 mg, 5 mmol) in THF (20 ml) cooled in an ice-water bath, a solution of amide (600 mg, 2.78 mmol) in THF (10 ml) was added dropwise during 10 min. The ice bath was removed and the reaction mixture was refluxed for 72 h. After cooling to room temperature, the reaction was carefully quenched with ethyl acetate (3 ml), and then diluted with water, the aqueous solution was acidified (dil. HCl) to pH 1 and extracted with dichloromethane (2×25 ml). The aqueous layer was then taken to pH 10 by addition of conc. sodium hydroxide (2 M) and the resulting turbid solution extracted with dichloromethane (4×50 ml). The combined dichloromethane solution was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography, yield=70%; ^{1}H NMR: δ 7.32–7.22 (m, 6H), 6.18 (d, J=1.7 Hz, 1H), 3.76 (s, 2H), 3.73 (s, 2H), 1.97 (s, 3H), 1.67 (br s, 1H); ^{13}C NMR: 148.88, 140.78, 140.0, 128.31, 128.13, 126.89, 116.27, 112.68, 52.69, 43.09, 9.75 ppm.

6.3.10. Methyl 2-[(benzylamino)methyl]-3-furoate (8e). To a mixture of methyl 2-(bromomethyl)-3-furoate (**26**)[26] (4.56 g, 20.8 mmol) and benzylamine (2.34 g, 21.88 mmol) in dry DMF (20 ml), was added potassium carbonate (2.88 g, 20.8 mmol) and the reaction mixture stirred at rt for 30 min until completion of the reaction (TLC). The reaction mixture was poured into ice-water mixture (100 ml). After separation of organic layer, the aqueous solution was extracted with ether (100 ml×2). The combined organic extracts were washed with water (50 ml), brine (25 ml×2), dried (anhydrous Na_2SO_4) and evaporated to result in 3.52 g of viscous oil. ^{1}H NMR spectrum of the crude product indicated two amines **8e** and **27** were formed in the ratio of 37:63 which were separated and purified by column chromatography. Yield=17%, ^{1}H NMR: 7.2–7.3 (m, 6H), 6.68 (br s, 1H), 4.10 (s, 2H), 3.79 (s, 3H), 3.76 (s, 2H), 2.09 (br s, 1H); ^{13}C NMR: 164.05, 160.58, 141.23, 139.72, 128.32, 128.16, 126.98, 114.62, 110.73, 52.91, 51.46, 44.60 ppm; HRMS calcd for $C_{14}H_{15}NO_3$: 245.10519. Found: 245.10467.

6.3.11. Methyl 2-[(benzyl{[3-(methoxycarbonyl)-2-furyl]-methyl}amino)methyl]-3-furoate 27. Yield=34%, ^{1}H NMR: 7.2–7.4 (m, 7H), 6.64 (br s, 2H), 4.11 (s, 4H), 3.76 (s, 2H), 3.73 (s, 6H); ^{13}C NMR: 163.93, 158.81, 141.72, 138.84, 128.80, 128.14, 126.98, 116.01, 110.62, 58.15, 51.36, 48.90 ppm; HRMS calcd for $C_{21}H_{21}NO_6$: 383.13688. Found: 383.13596.

6.4. Representative procedure for the reaction of *N*-benzylfurfurylamines with citraconic anhydride and subsequent IMDA reaction in benzene at 65°C

6.4.1. 3-Benzyl-5-methyl-4-oxo-10-oxa-3-azatricyclo [5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6a). To the stirred solution of *N*-benzyl furfurylamine **5a** (1.87 g, 10 mmol) in benzene (15 ml) was added a solution of citraconic anhydride (1.12 g, 1 mmol) in benzene (5 ml) was added at rt. The solution was then heated for 24 h, in an oil-bath maintained at 65°C. After completion of the reaction, the reaction mixture was cooled to rt to allow the cycloadduct to crystallize. The product was filtered and washed with benzene (5 ml) to yield 90% of analytically pure cycloadduct **6a**, mp: 147–148°C; ^{1}H NMR: δ 7.36–7.22 (m, 5H), 6.55 (dd, *J*=5.7, 1.6 Hz, 1H), 6.38 (d, *J*=5.7 Hz, 1H), 5.22 (d, *J*=1.5 Hz, 1H), 4.73 (d, *J*=14.9 Hz, 1H), 4.33 (d, *J*=14.9 Hz, 1H), 3.65(AB q, *J*=11.9 Hz, 2H), 2.39 (s, 1H), 1.23 (s, 3H); ^{13}C NMR: 175.6, 174.1, 137.7, 135.7, 133.1, 128.9, 128.0, 127.8, 91.0, 81.7, 56.4, 53.7, 47.0, 46.8, 21.8 ppm; elemental analysis calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.32; H, 5.69; N, 4.74.

6.4.2. 5-Methyl-3-(2-methylbenzyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6b). Yield=70%; mp: 164–165°C; ^{1}H NMR: δ 7.22–7.17 (m, 4H), 6.56 (dd, *J*=5.7, 1.7 Hz, 1H), 6.38 (d, *J*=5.7 Hz, 1H), 5.24 (d, *J*=1.7 Hz, 1H), 4.65 (d, *J*=14.8 Hz, 1H), 4.47 (d, *J*=14.8 Hz, 1H), 3.63 (d, *J*=12.1 Hz, 1H), 3.53 (d, *J*=12.1 Hz, 1H), 2.40 (s, 1H), 2.29 (s, 3H), 1.23 (s, 3H); ^{13}C NMR: 175.09, 174.17, 137.69, 137.04, 133.30, 133.06, 130.73, 129.16, 128.07, 126.23, 90.98, 81.71, 56.47, 53.75, 46.87, 45.13, 21.91, 19.02 ppm.; elemental analysis calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.00; H, 5.98; N, 4.54.

6.4.3. 3-(2-Hydroxybenzyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6c). Yield=83%; mp: 163–164°C; ^{1}H NMR: δ (acetone-D$_6$): 7.23–7.11 (m, 2H), 6.85–6.77 (m, 2H), 6.58 (s, 2H), 5.01 (s, 1H), 4.55 (d, *J*=15.0 Hz, 1H), 4.33 (d, *J*=15.0 Hz, 1H), 4.00 (d, *J*=11.9 Hz, 1H), 3.68 (d, *J*=11.9 Hz, 1H), 2.26 (s, 1H), 1.13 (s, 3H) ppm;^{13}C NMR (CD_3OD): 177.15, 175.99, 156.84, 138.49, 134.73, 130.76, 129.98, 123.28, 120.75, 116.30, 92.28, 82.82, 58.40, 54.12, 50–45 shielded, 42.72, 21.85; elemental analysis calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.54; H, 5.45; N, 4.45

6.4.4. 3-(2-Methoxybenzyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6d). Yield=66%; mp: 159–160°C; ^{1}H NMR: δ 7.32–7.19 (m, 2H), 6.96–6.87 (m, 2H), 6.60 (dd, *J*=5.7,1.8 Hz, 1H), 6.36 (d, *J*=5.7 Hz, 1H), 5.33 (d, *J*=1.7 Hz, 1H), 4.70 (d, *J*=14.6 Hz, 1H), 4.45 (d, *J*=14.6 Hz, 1H), 3.82 (s, 3H), 3.70 (d, *J*=12.2 Hz, 1H), 3.62 (d, *J*=12.2 Hz, 1H), 2.44 (s, 1H),1.20 (s, 3H); ^{13}C NMR: 175.84,173.41, 157.62, 137.83, 132.91, 130.06, 121.29, 123.45, 120.86, 110.40, 91.26, 82.12, 55.82, 55.34, 54.33, 47.32, 42.05, 21.95 ppm; elemental analysis calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.87; H, 5.71; N, 4.36.

6.4.5. 3-(4-Methoxybenzyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6e). Yield=72%; mp: 145°C; ^{1}H NMR: δ 7.32–7.19 (m, 2H), 6.96–6.87 (m, 2H), 6.60 (dd, *J*=5.7,1.7 Hz, 1H), 6.36 (d, *J*=5.7 Hz, 1H), 5.33 (d, *J*=1.7 Hz, 1H), 4.70 (d, *J*=14.6 Hz, 1H), 4.45 (d, *J*=14.6 Hz, 1H), 3.82 (s, 3H), 3.70 (d, *J*=12.2 Hz, 1H), 3.62 (d, *J*=12.2 Hz, 1H), 2.44 (s, 1H), 1.20 (s, 3H); ^{13}C NMR: 175.71, 173.72, 159.28, 137.83, 132.97, 129.62, 129.42, 114.33, 91.11, 81.96, 56.23, 55.34, 53.99, 46.91, 46.34, 21.88 ppm; elemental analysis calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.58; H, 5.85; N, 4.23.

6.4.6. 3-(4-Nitrobenzyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6f). Yield=57%; mp: 154–155°C; ^{1}H NMR: δ 8.20 (d, *J*=8.6 Hz, 2H), 7.43 (d, *J*=8.6 Hz, 2H), 6.57 (dd, *J*=5.7,1.7 Hz, 1H), 6.44 (d, *J*=5.7 Hz, 1H), 5.19 (d, *J*=1.7 Hz, 1H), 4.73 (d, *J*=15.7 Hz, 1H), 4.53 (d, *J*=15.7 Hz, 1H), 3.80 (d, *J*=11.6 Hz, 1H), 3.61 (d, *J*=11.6 Hz, 1H), 2.38 (s, 1H), 1.25 (s, 3H); ^{13}C NMR: 175.68, 174.49, 147.58, 143.35, 137.73, 133.11, 128.56, 124.15, 90.99, 81.52, 56.66, 53.33, 47.24, 46.09, 21.64 ppm; elemental analysis calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 58.89; H, 4.63; N, 8.04.

6.4.7. 3-(2-Naphthylmethyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6g). Yield=83%; mp168–169°C; ^{1}H NMR: δ 7.85–7.80 (m, 3H), 7.70 (s, 1H), 7.50–7.47 (m, 2H), 7.34 (dd, *J*=8.4,1.7 Hz, 1H), 6.56 (dd, *J*=5.7, 1.7 Hz, 1H), 6.36 (d, *J*=5.7 Hz, 1H), 5.26 (d, *J*=1.7 Hz, 1H), 4.91 (d, *J*=14.7 Hz, 1H), 4.47 (d, *J*=14.7 Hz, 1H), 3.71 (d, *J*=11.9 Hz, 1H), 3.63 (d, *J*=11.9 Hz, 1H), 2.42 (s, 1H), 1.24 (s, 3H); ^{13}C NMR: 176.20, 173.06, 137.97, 133.40, 132.98, 132.82, 129.09, 127.88, 127.81, 127.39,. 127.22, 126.51, 126.28, 125.77, 91.34, 82.24, 77.30, 55.91, 54.44, 47.21, 22.09 ppm; elemental analysis calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.15; H, 5.29; N, 4.11.

6.4.8. 3-Cyclohexyl-5-methyl-4-oxo-10-oxa-3-azatricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (6h). Yield=76%; mp: 165–167°C; ^{1}H NMR: δ 6.67 (dd, *J*=5.7,1.7 Hz, 1H), 6.42 (d, *J*=5.7 Hz, 1H), 5.29 (s, 1H), 3.92 (m, 1H), 3.78 (d, *J*=12.0 Hz, 1H), 3.72 (d, *J*=12.0 Hz, 1H), 2.41 (s, 1H), 1.80–1.66 (m, 5H), 1.44–1.29 (m, 5H), 1.20 (s, 3H); ^{13}C NMR: 175.17, 173.49, 137.62, 132.89, 91.0, 81.79, 56.23, 53.92, 50.84, 43.36, 29.99, 29.60, 25.23, 25.07, 21.89 ppm; elemental analysis calcd for $C_{16}H_{219}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.91; H, 7.32; N, 4.87.

6.4.9. 3-Benzyl-6-methyl-9-(methylsulfanyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (9a). Yield=80%; mp: 178–180°C; ^{1}H NMR: δ 7.37–7.21 (m, 5H) 5.85 (d, *J*=2.0 Hz, 1H), 5.28 (d, *J*=2.0 Hz, 1H), 4.59 (d, *J*=14.9 Hz,1 H), 4.49 (d, *J*=14.9 Hz, 1H), 3.71 (d, *J*=12.1 Hz, 1H), 3.50 (d, *J*=12.1, 1H), 2.48 (s, 1H), 2.33 (s, 3H), 1.33 (s, 3H); ^{13}C NMR: 174.88,172.45, 146.47, 135.19, 129.21, 128.26, 128.21, 122.05, 91.29, 86.47, 58.55, 55.96, 47.29, 24.05, 15.61 ppm; elemental analysis calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05; S, 9.28. Found: C, 62.23; H, 5.51; N, 4.11; S, 9.03.

6.4.10. 3-Benzyl-5-methyl-8-(methylsulfanyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (10b). Yield=92%; mp:178–179°C; ^{1}H NMR: δ 7.35–7.21 (m, 5H), 5.79 (s, 1H), 5.03 (s, 1H), 4.73 (d, *J*=14.9 Hz, 1H), 4.29 (d, *J*=14.9 Hz, 1H), 3.62 (d, *J*=11.9 Hz, 1H), 3.55 (d, *J*=11.9 Hz, 1H), 2.44 (s, 1H), 2.29 (s, 3H), 1.21 (s, 3H); ^{13}C NMR: 175.53, 173.75, 149.53, 135.68, 128.03, 127.84, 119,72, 92.48, 83.89, 58.69, 54.17, 47.02, 46.87, 21.92, 15.43 ppm; elemental analysis calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05; S, 9.28. Found: C, 62.21; H, 5.57; N, 4.09; S, 9.01.

6.4.11. 3-Benzyl-5,9-dimethyl-4-oxo-10-oxa-3-azatricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (10c). Yield=82%;

mp: 164–165°C; ^{1}H NMR: δ 7.37–7.23 (m, 5H), 6.13 (t, *J*=1.7 Hz, 1H), 5.09 (s, 1H), 4.73 (d, *J*=14.9 Hz, 1H), 4.35 (d, *J*=14.9 Hz, 1H), 3.66 (d, *J*=11.9 Hz, 1H), 3.53 (d, *J*=11.9 Hz, 1H), 2.44 (s, 1H), 1.85 (d, *J*=1.5 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR: 175.86, 173.67, 143.27, 135.64, 130.56, 129.02, 128.08, 127.93, 92.42, 81.09, 56.36, 54.53, 47.03, 45.89, 21.48, 14.19 ppm; elemental analysis calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.92; H, 6.09; N, 4.41.

6.4.12. 3-Benzyl-5,7-dimethyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (10d). Yield=92%; mp: 124–125°C; ^{1}H NMR: δ 7.26–7.24 (m, 5H), 6.40 (d, *J*=5.6 Hz, 1H), 6.28 (d, *J*=5.6 Hz, 1H), 4.88 (d, *J*=14.8 Hz, 1H), 4.22 (d, *J*=14.8 Hz, 1H), 3.60 (s, 3H), 2.3 (s, 1H), 1.68 (s, 3H), 1.28 (s, 3H); ^{13}C NMR: 175.51, 172.87, 140.61, 136.09, 134.35, 128.88, 128.20, 127.75, 90.33, 88.91, 59.88, 56.69, 47.32, 46.93, 21.88, 16.13 ppm; elemental analysis calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.46; H, 6.46; N, 4.57.

6.4.13. 3-Benzyl-9-(methoxycarbonyl)-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (10e). Yield=72%, mp: 133–134°C, ^{1}H NMR: 7.22–7.34 (m, 6H), 5.29 (br s, 1H), 4.61 (d, *J*=14.9 Hz, 1H), 4.48 (d, 14.9 Hz, 1H), 4.36 (d, *J*=12.2 Hz), 3.75 (s, 3H), 3.54 (d, *J*=12.2 Hz), 2.45 (s, 1H), 1.26 (s, 3H); ^{13}C NMR: 174.95, 172.70, 162.99, 146.39, 138.26, 135.29, 128.91, 128.32, 127.92, 91.32, 80.98, 56.09, 52.98, 52.12, 46.94, 45.96, 21.45 ppm; elemental analysis calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.63; H, 5.71; N, 3.73.

6.4.14. 3-Benzyl-6-methyl-4-oxo-10-oxa-3-azatricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (7). Yield=30%; mp:131–132°C; ^{1}H NMR: δ 7.36–7.22(m, 5H), 6.53–6.48 (m, 2H), 5.3 (d, *J*=1.1 Hz, 1H), 4.54 (AB q, *J*=14.8 Hz, 2H), 3.82 (d, *J*=12.1 Hz, 1H), 3.62 (d, *J*=12.1 Hz, 1H), 2,46 (s, 1H), 1.33 (s, 3H); ^{13}C NMR: 174.8, 172.6, 136.1, 135.4, 135.2, 129.0, 128.2, 128.1, 89.7, 85.7, 58.2, 53.3, 48.8, 47.1, 23.6 ppm; elemental analysis calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.04; H, 5.68; N, 4.75.

6.4.15. 3-Benzyl-6-methyl-8-(methylsulfanyl)-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (9b). Yield=10%; ^{1}H NMR: δ 7.36–7.24 (m, 5H), 5.90(s,1H), 5.19 (s, 1H), 4.64 (d, *J*=14.8 Hz, 1H), 4.43 (d, *J*=14.8 Hz, 1H), 3.75 (d, *J*=12.1 Hz, 1H), 3.57 (d, *J*=12.1 Hz, 1H), 2.56 (s, 1H), 2.30 (s, 3H), 1.46 (s, 3H); ^{13}C NMR: 174.78, 172.90, 148.76, 135.15, 129.03, 128.15, 128.08, 121.92, 90.69, 88.17, 58.95, 54.26, 49.04, 47.12, 23.66, 15.25 ppm; elemental analysis calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.05; S, 9.28. Found: C, 62.27; H, 5.39; N, 4.23; S, 8.85.

6.4.16. 3-Benzyl-6,9-dimethyl-4-oxo-10-oxa-3-azatricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (9c). Yield=22%; mp: 144–145°C; ^{1}H NMR: δ 7.35–7.13 (m, 5H), 6.04 (s, 1H), 5.13 (s, 1H), 4.60, 4.55, 4.53, 4.48 (ABq, 2H), 3.72 (d, *J*=12.1 Hz, 1H), 3.52 (d, *J*=12.1 Hz, 1H), 2.38 (s, 1H), 1.86 (d, *J*=1.5 Hz, 3H), 1.31 (s, 3H); ^{13}C NMR: 174.80, 172.38, 144.86, 135.25, 129.03, 128.66, 128.19, 128.04, 91.07, 85.19, 57.82, 54.87, 47.25, 47.13, 23.48, 12.25 ppm; elemental analysis calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.87; H, 6.21; N, 4.56.

6.4.17. 8-Ethyl 6-methyl 3-benzyl-6-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6,8-dicarboxylate (11). To stirred solution of furfurylamine **8f** (103 mg, 0.4 mmol) in benzene (1 ml), was added citraconic anhydride (45 mg, 0.4 mmol) in benzene (1 ml) and the reaction mixture was stirred at rt for 2 h. After removal of benzene under reduced pressure, the resulting viscous oil was diluted with dry methanol (2 ml). To the methanolic solution an etherial solution of diazomethane was added until a faint yellow colour persisted (*caution*). Excess diazomethane was removed by bubbling argon through the reaction mixture, followed by removal of solvent under reduced pressure. The reaction mixture was then diluted with dichloromethane (2.2 ml) and transferred to a 2.5 ml Teflon vessel which was compressed to 11 kbar at 40°C for 12 h. After decompression and removal of the solvent the reaction mixture was chromatographed to get diasteromers **11** and **12** in the ratio of 1:2; diester **11**: viscous oil; Yield=17%, ^{1}H NMR: 7.20–7.39 (m, 6H), 5.29 (s, 1H), 4.56 (d, *J*=14.8 Hz, 1H), 4.43 (d, *J*=14.8 Hz, 1H), 4.33–4.17 (m, 2H), 3.79 (s, 3H), 3.77 (d, *J*=11.6 Hz, 1H), 3.61 (d, *J*=11.6 Hz, 1H), 2.46 (s, 1H), 1.29 (t, *J*=7.1 Hz, 3H), 1.29(s, 3H); ^{13}C NMR: 173.33, 170.10, 162.33, 143.63, 143.41, 135.73, 128.84, 127.84, 127.72, 89.95, 84.56, 61.11, 58.15, 52.57, 50.91, 48.21, 46.51, 21.59, 14.18 ppm; HRMS calcd for $C_{21}H_{23}NO_6$: 385.15253. Found: 385.15204.

6.4.18. 8-Ethyl 6-methyl 3-benzyl-5-methyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6,8-dicarboxylate (12). Viscous oil; Yield=34%, ^{1}H NMR: 7.21–7.35 (m, 5H), 7.12 (s, 1H), 5.30 (s, 1H), 4.72 (d, *J*=14.9 Hz, 1H), 4.26 (d, *J*=14.9 Hz, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 3.82 (s, 3H), 3.69 (d, *J*=11.5 Hz, 1H), 3.59 (d, *J*=11.5 Hz, 1H), 2.40 (s, 1H), 1.30 (t, *J*=7.1 Hz, 3H), 1.22(s, 3H); ^{13}C NMR: 173.61, 171.77, 161.78, 143.52, 142.05, 135.79, 128.80, 127.83, 127.60, 91.86, 80.54, 61.18, 57.93, 52.50, 52.27, 46.57, 46.48, 21.08, 14.15 ppm; HRMS calcd for $C_{21}H_{23}NO_6$: 385.15253. Found: 385.15236.

6.4.19. Dimethyl 11-benzyl-9-methyl-10-oxo-13-oxa-3,4,11-triazatetracyclo[5.5.1.0^{1,9}.0^{2,6}]tridec-3-ene-2,8-dicarboxylate (13). An etheral solution of diazomethane was added to a solution of carboxylic acid **10e** (100 mg, 0.28 mmol) in dry methanol (10 ml) until the faint yellow color of diazomethane persisted. Excess diazomethane was quenched with acetic acid and the solvent was removed. The resulting diester **13** was obtained as a white crystalline solid after purification by column chromatography. Yield=90%, mp: 69°C, ^{1}H NMR: 7.19–7.34 (m, 5H), 4.82 (dd, *J*=18.7, 8.4 Hz, 1H), 4.72 (dd, *J*=18.7, 3 Hz, 1H), 4.52 (d, *J*=15 Hz, 1H), 4.44 (d, *J*=15 Hz, 1H), 4.35 (s, 1H), 4.35 (d, *J*=11.7 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.50 (d, *J*=11.7 Hz, 1H), 2.74 (dd, *J*=8.4, 3 Hz, 1H), 2.68 (s, 1H), 1.44 (s, 3H); ^{13}C NMR: 173.14, 170.95, 165.49, 135.55, 128.82, 127.84, 127.72, 108.23, 90.95, 85.68, 83.49, 58.90, 57.28, 53.27, 52.23, 46.68, 45.57, 41.92, 19.72 ppm; HRMS calcd for $C_{21}H_{23}N_3O_6$: 413.15868. Found: 413.15848.

6.4.20. Dimethyl 3-benzyl-5-methyl-4-oxo-10-oxa-3-azatricyclo [5.2.1.0^{1,5}]dec-8-ene-6,9-dicarboxylate (14). To a solution of ester-acid **10e** (678 mg, 1.9 mmol) in dry methanol (5 ml) under a blanket of Ar at 0°C was added thionyl chloride (226 mg, 1.9 mmol) dropwise and the reaction mixture was stirred for 12 h. After removal of methanol under reduced pressure, the reaction mixture was taken in dichloromethane (30 ml), which was washed with water (20 ml), sat. sodium bicarbonate solution (15 ml), brine (2×20 ml) and dried over Na_2SO_4. Removal of the solvent resulted in crude diester **14** which was purified by chromatography; Yield=30%; viscous oil; ^{1}H NMR: 7.18–7.36 (m, 6H), 5.15 (d, *J*=1.5 Hz, 1H), 4.61 (d, *J*=15.0 Hz, 1H), 4.40 (d, *J*=15.0Hz, 1H), 4.31 (d, *J*=12.0 Hz, 1H), 3.41 (d, *J*=12.0 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 2.33 (s, 1H), 1.23 (s, 3H); ^{13}C NMR: 173.50, 171.81, 163.0, 146.0, 138.20, 135.91, 128.77, 127.77, 127.59, 90.99, 79.94, 56.64, 52.34, 52.06, 51.70, 46.55, 45.61, 20.96 ppm; HRMS calcd for $C_{20}H_{21}NO_6$: 371.13688. Found: 371.13644.

6.4.21. 6-Ethyl 8-methyl 11-benzyl-9-methyl-10-oxo-13-oxa-4,5,11-triazatetracyclo[5.5.1.0^{1,9}.0^{2,6}]tridec-4-ene-6,8-dicarboxylate (16). Following the procedure described previously, the reaction of a mixture of carboxylic acids **9f** and **10f** (52 mg) with excess diazomethane furnished a mixture of diesters from which the major isomer **16** could be isolated by column chromatography in 42% yield; mp: 59–60°C, ^{1}H NMR: 7.16–7.34 (m, 5H), 5.06 (s, 1H), 4.66 (dd, *J*=18.4, 4.5 Hz, 1H), 4.43 (dd, *J*=18.4, 1.8 Hz, 1H), 4.36 (qd, *J*=7.1 and 1.5 Hz, 2H), 4.60 (d, *J*=15.0 Hz, 1H), 4.30 (d, *J*=15.0 Hz, 1H), 3.79 (s, 3H), 3.35 (d, *J*=11.4 Hz, 1H), 3.26 (d, *J*=11.4 Hz, 1H), 2.86 (dd, *J*=4.4, 1.8 Hz, 1H), 2.77 (s, 1H), 1.41 (s, 3H), 1.37 (t, *J*=7.1 Hz, 3H); ^{13}C NMR: 174.0, 170.65, 165.95, 135.56, 128.93, 127.84, 127.81, 111.63, 92.11, 81.52, 80.27, 60.94, 58.41, 53.41, 52.40, 46.53, 45.63, 36.86, 18.91, 14.17 ppm; HRMS calcd for $C_{22}H_{25}N_3O_6$: 427.17433. Found: 427.17456.

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