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Synthesis of Substituted Benzo[*b*]indolizidines and Benzo[*b*]-quinolizidines *via* Ring-Opening of 3-Bromo-2,5-dimethylthiophene-1,1-dioxide

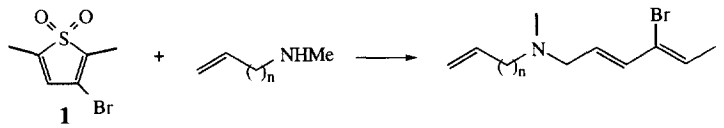
Anders Tsirk, Salo Gronowitz* and Anna-Britta Hörnfeldt

Organic Chemistry 1, Chemical Center, University of Lund, P. O. Box 124, S-221 00 Lund, Sweden.

Abstract: A new method for the preparation of benzo[*b*]indolizidines and benzo[*b*]quinolizidines based on two reactions: an amine induced ring-opening of 3-bromo-2, 5- dimethylthiophene-1,1-dioxide (**1**) with 2-allyl-pyrrolidine (**2**), 2-allylpiperidine (**3**), 2-[2-(1',3'-dithiolan)methyl]pyrrolidine (**4**) and 2-[2-(1'- 3'-dithiolan)methyl]piperidine (**5**); and an intramolecular Diels-Alder reaction, is described.

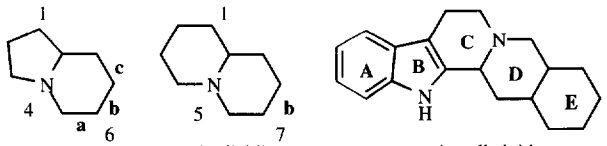
Introduction

The amine induced ring-opening reaction of thiophene-1,1-dioxides, and its ability to give different dienic systems, was reported by us in 1987.[1] Numerous dioxides and amines have been investigated in this reaction[2] and recently we found that the most intriguing results were obtained when elaborating the amines. Using secondary amines with an ω-unsaturated side chain, trienes were obtained (Scheme 1),[3] which in a subsequent step could undergo an intramolecular Diels-Alder reaction (IMDA) to give polyhydroisoindoles or polyhydroisoquinolines in excellent yields.[4]



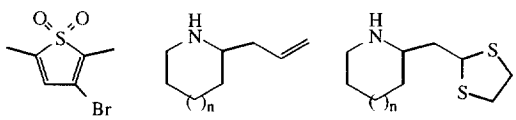
Scheme 1. n = 1, 2, 3; toluene, Ar, 100 °C, 5-17 h

The aim of the research detailed in this paper was primarily to apply α-substituted cyclic amines to ring-open **1** and secondly to investigate if the stereoselectivity could be controlled in the subsequent IMDA. Here we present exploratory work addressing a new general method for the synthesis of various substituted indolizidines and quinolizidines, substructures found in both classes A and B of the alkaloids detected in skin extracts from dendrobatid frogs.[5,6] The benzo[*b*]quinolizidine structure also occurs in the Rauwolfia alkaloids, *i.e.* it constitutes the C-, D- and E-rings of reserpine alkaloids.[7]As many of these alkaloids show pronounced biological activity, they are of potential pharmacological use [8-10] and therefore attractive targets for synthesis.[11-13]



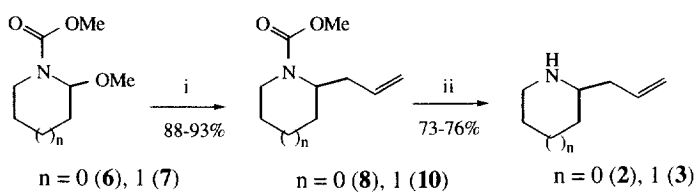
Results and Discussion

Methods for the α-substitution of pyrrolidines and piperidines, developed by Shono,[14-18] gave us easy access to relevant amines.We decided to utilize racemic pyrrolidines and piperidines for methodological studies, knowing that the routes of Shono's, Wistrand's[19-23]and Pedregal's[24,25] could provide an abundance of enantiopure amines. The amines 2-allylpyrrolidine (**2**), 2-allyl-piperidine (**3**), 2-[2-(1',3'-dithiolan)-methyl]-pyrrolidine (**4**) and 2-[2-(1',3'-dithiolan)methyl]piperidine (**5**) (Scheme 2) enabled us to synthesize new trienes, which in an IMDA yielded the tricyclic benzo[*b*]indolizidine and benzo[*b*]quinolizidine systems described below.



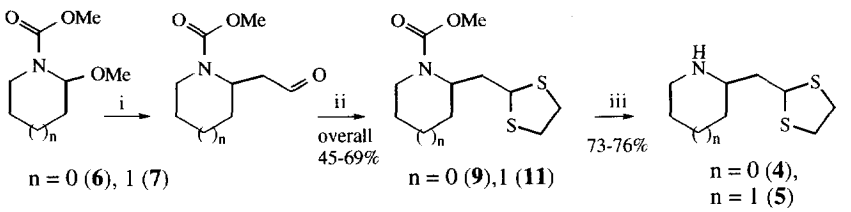
Scheme 2.

2-Methoxy-1-carboxymethylpyrrolidine (**6**) or -piperidine (**7**), obtained from the carbamates through anodic methoxylation, were treated with $TiCl_4$ and either allyl trimethylsilane or vinyl acetate at -78 °C, thus giving the corresponding α-substituted 1-carboxymethyl pyrrolidines **8** and **9** or piperidines **10** and **11** in good yields (Schemes 3 and 4).[15] Carbamate cleavage was achieved by using iodotrimethylsilane.[26]



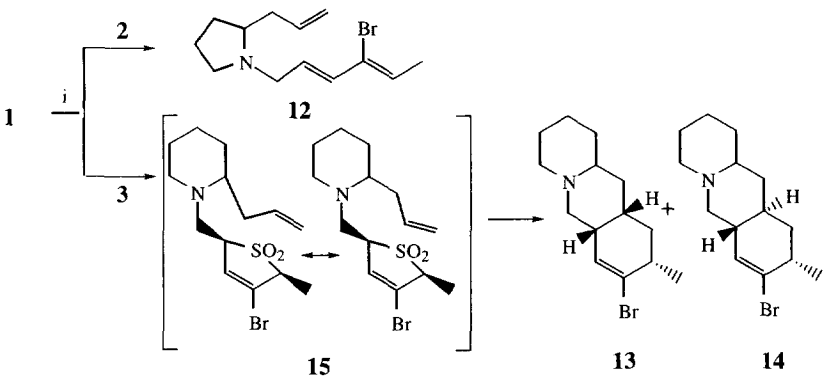
Scheme 3. i. $TiCl_4$, allyl trimethylsilane/CH_2Cl_2, -78 °C.
ii. 1.Me_3SiI/$CHCl_3$, 50 °C. 2. MeOH/MeONa.

Attacking the *N*-acyliminium ions with vinyl acetate gave aldehydes, which were best protected as crude products by ethanedithiol using a catalytic amount of $TiCl_4$ (Scheme 4).[27] A method which utilized $TeCl_4$ also proved to work.[28] Better overall yields (>70 %) of **4** and **5** could be achieved through ozonolysis[22] of **8** or **10** followed by thioacetal protection, but at a higher cost.



Scheme 4. i. $TiCl_4$, vinyl acetate/CH_2Cl_2, -78 °C. ii. ethane-1,2-dithiol, $TiCl_4$, r.t.. iii. 1.$Me_3SiI/CHCl_3$, 50 °C. 2. MeOH/MeONa.

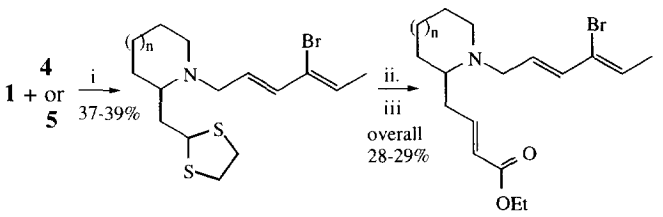
Four equivalents of amine were reacted with **1** in toluene at 100 °C.[1] The reaction with **2** led to triene formation and (*2E,4Z*)-1-(2-allylpyrrolidino)-4-bromo-2,4-hexadiene (**12**) was isolated in 24 % yield. Four other minor components were also formed: an isomer to **12**, a debrominated triene (isolated in 7 %), and two IMDA products. No triene could be isolated from the reaction of **3**, but instead the IMDA products *cis* and *trans*- 6a,9,10, 10a-tetrahydro-8-bromo-9-methylbenzo[*b*]quinolizidine (**13** and**14**) were formed directly and were isolated from the reaction mixture in 14 % and 11.5 % yield, respectively (*cis*:*trans* ratio, 55:45) (Scheme 5). A 12.9 % yield of debrominated IMDA product was also recovered.



Scheme 5. i. toluene, Ar, 100 °C, 5-7.5 h, yields 24-25.5 %.

These results might be interpreted in two ways: either the reaction proceeds stepwise, where the intermediate piperidino substituted sulfolene (**15**) undergoes a disrotatory cheletropic elimination of SO_2 to form a triene, which then cyclizes in an IMDA; or the reaction is concerted, with the extrusion of SO_2 taking place simultaneously with the IMDA. There is some support for the latter assumption: the thermodynamics should favor a concerted rather than a stepwise reaction.[29] On the other hand, we do not know for sure that we have an intermediate like **15**. Clearly, all isolated trienes and dienes have been formed stereoselectively by the same mechanism and are *EE* in regard to the carbon chain. If we look at 2,5-disubstituted *cis*-3-sulfolenes, they are thermodynamically more stable, and they undergo disrotatory cheletropic elimination faster than the corresponding *trans* compounds, and their diene formation shows a 100 % *EE* selectivity ; [30,31] furthermore, isomerization of *trans* sulfolenes to *cis* sulfolenes in the presence of a base has also been seen.[32] Thus all the examples available to date are in agreement with a *cis* sulfolene structure of the intermediate. The difference between the reactivities of **2** and **3** would seem to be due to geometrical constraints affecting the availability of a conformation allowing an IMDA, as only a few percent of IMDA products were detected in the former case.

Slower reactions with better yields were generally observed when a bulky substituent such as the 1'-3'-dithiolan-methyl group was in position 2 of the reacting amine. Compound **4** gave 39 % of (*2E,4Z*)-1-[2-(1',3'-dithiolan)methyl]pyrrolidino-4-bromo-2,4-hexadiene (**16**) while **5** gave 37 % of (*2E,4Z*)-1-[2- (1',3'-dithiolan)methyl]piperidino-4-bromo-2,4-hexadiene (**17**) (Scheme 6):

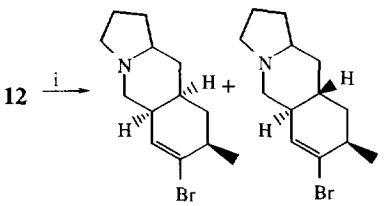


n = 0 (**16**), n = 1 (**17**) n = 0 (**18**), n = 1 (**19**)

Scheme 6. i. toluene, Ar, 100 °C, 27-70 h. ii. HgO/HBF_4,THF/H_2O, 30 min. iii. $(Ph)_3P$=CHCOOEt, CH_2Cl_2, r.t..

The complexity of the reaction mixture in these two cases precluded any identification of by-products. Deprotection of the aldehyde function proved to be harder than expected. Several of the mildest reagents available for removal of the 1',3'-dithiolan group were investigated (clayfen[33], claycop[33] and $(F_3CCOO)_2PhI$[34]) but they all led to total decomposition of the starting material. Finally, treating **16** or **17** with HgO and aqueous HBF_4 in THF generated the aldehyde in modest yield.[35] After a brief work-up this was reacted with $(Ph)_3P$=CHCOOEt at ambient temperature yielding (*2E,4Z*)-1-[2-(ethylbut-2-enoyl)-pyrrolidino]-4-bromo-2,4-hexadiene (**18**) in 28 % and (*2E,4Z*)-4-bromo-1-[2-(ethylbut-2-enoyl)piperidino]-2,4-hexadiene (**19**) in 29 % overall yield from **16** or **17**. An important reason for choosing 1'-3'-dithiolane as protective group, was to have the option of alkylating the methine carbon before converting it to a carbonyl carbon. However, if this option is redundant, it should be possible to protect the aldehyde as a 1',3'-dioxolan group, which generally is more readily removed.[36[1]]

The thermal IMDA took place at 150 °C or at 100 °C in toluene under argon; **12** gave 91 % of *cis* and *trans*-5a, 8, 9, 9a-tetrahydro-7-bromo-8-methylbenzo[b]-indolizidine (**20** and **21**) in a *cis/trans* ratio of 55:45 after 26 h (Scheme 7).



20:**21** (55:45)

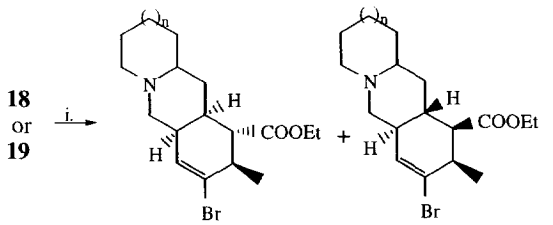
Scheme 7. i. toluene, Ar, 150 °C, 26 h, 91 %

In order to improve the stereoselectivity of the IMDA we tried an approach from Livinghouse's group. They had succeeded in performing [4+2] like cycloadditions on otherwise unactivated trienes with either an oxygen or an amide nitrogen in the chain, by using a rhodium(I) catalyst, $[(CF_3)_2CHO)_3P]_2RhCl$, generated *in*

[1] In this case the carbamate cleavage cannot be made by Me_3SiI: see M. J. Jung, W. A. Andrus, P. L. Ornstein, *Tetrahedron Lett.* **1977**, *18*, 4175-4178. Rather, hydrazine should be used: see reference 36.

situ from [RhCl(cyclooctene)$_2$]$_2$ and four equivalents of tris- (1,1,1,3,3,3-hexafluoropropoxy)phosphite.[37] We hoped that if our triene would undergo the same reaction, a careful choice of chiral ligands could make the cyclization enantioselective as well as stereoselective. We used (*2E,4Z*)-1-amino-4-bromo-*N*-methyl-*N*-(1-prop-2-enyl)-2,4-hexadiene[3] as a probe together with 0.1-1.2 equivalents of Rh(I) in both anhydrous THF and TFE with temperatures ranging from 55 to 65 °C for up to three days. However, no cyclization was observed, probably due to strong coordination of the substrate – a tertiary amine – to Rh(I).

At 100 °C **18** gave *cis*- and *trans*-9-carboxyethyl-5a, 8, 9, 9a-tetrahydro-7-bromo-8-methylbenzo-[*b*]indolizidine (**22** and **23**) in a *cis:trans* ratio of 73:27 and **19** gave *cis*- and *trans*-8-bromo-10-carboxyethyl-6a,9,10,10a-tetrahydro-9-methylbenzo[*b*]quinolizidine (**24** and **25**) in a *cis:trans* ratio of 70:30 after 17 h; both reactions gave nearly quantitative yields (Scheme 8). The same reactions performed at 150 °C gave a *cis:trans* ratio of 62:38 in 82 % yield for **18** and in 97 % yield for **19**, which indicates a temperature dependence of the stereoselectivity.



Scheme 8. i. toluene, Ar, 100°C, 17h, quantitative yields;
n=0, cis:trans 73:27, **22**:**23**; n=1, cis:trans 70:30, **24**:**25**.

The following Lewis acids were evaluated for catalysis in the IMDA: $EtAlCl_2$, Et_2AlCl and $TiCl_4$;[38,39] the best results were obtained with the latter, of which two equivalents were required for a complete conversion of **18** and **19** at room temperature in dry CH_2Cl_2 under an argon atmosphere. Yields were quantitative and excellent stereoselectivities were observed: the *trans* fused IMDA products were formed in 93 to 95 % yield and the *cis* fused in 7 to 5 % yield (Table).

Table. Yields and selectivities obtained after thermal and $TiCl_4$ catalyzed IMDA.

conditions/ °C	substrate	products	yield/ %	*cis:trans* ratio
150	**12**	**20,21**	91	55:45
100	**1+3**	**13,14**	26	55:45
150	**18**	**22,23**	82	62:38
150	**19**	**24,25**	97	62:38
100	**18**	**22,23**	quant.	73:27
100	**19**	**24,25**	quant	70:30
$TiCl_4$, r.t.	**18**	**22,23**	quant.	6:94
$TiCl_4$, r.t.	**19**	**24,25**	quant	6:94

It is interesting to note the complete reversal of stereoselectivity going from the termal to the Lewis acid-catalyzed IMDA. The predominance of *trans* products in Lewis acid-catalyzed IMDAs has also been observed in decatrienic systems with a carbon atom instead of a nitrogen atom in the tether. Electronic factors are

believed to be responsible for this change as the double bond of the dienophile is polarized when the Lewis acid coordinates to the carbonyl oxygen.[40] The selectivities of the thermal IMDAs differ more: no selectivity is found for comparable carbon decatrienes.[40] Therefore we believe that geometrical factors also play an important role in the stereochemical outcome of our IMDAs. We made some preliminary calculations using the PM3 force field,[41] to see to what extent the transition state (TS) energies of the IMDA were altered by $TiCl_4$ coordinating to the nitrogen. In our models we calculated a N–$SiCl_3$ coordination and found that the energy difference between the *cis* TS and the *trans* TS diminished significantly when the coordination took place, as compared to the uncoordinated TSs. Thus, the geometries of the TSs seemed to be altered in favour of the trans TS as the nitrogen atom became tetracoordinated, which implies that tetracoordinated aza decatrienes would give product ratios similar to those found for carbon decatrienes.

Conclusions

The most important observation is that the ring-opening reaction works when using amines with bulky α-substituents. It also retains its stereoselectivity: only (*E,E*)-dienes in regard to the carbon chain are formed. We only partly succeeded in making the subsequent IMDA stereoselective; but where it worked we could control the selectivity to obtain either 70 % of the *cis* or 94 % of the *trans* fused product. In view of the qualities shown, we believe that further efforts in developing and elucidating this new synthetic pathway will prove worthwhile.

Experimental

The ^1H NMR, ^{13}C NMR, COSY-45 and HETCOR spectra were recorded on a Varian XL300-spectrometer, while the gradient COSY and the NOESY spectra were recorded on a Bruker ARX500 instrument; $CDCl_3$ was consistently used as solvent using residual $CHCl_3$ as reference (7.27 ppm). The mass spectra were recorded on a JEOL-SX 102 mass spectrometer at 70 eV. GLC analyses were carried out on a Varian 3600 gas chromatograph equipped with a SPB5 capillary column. The IR spectra were recorded on a Perkin Elmer 298 infrared spectrophotometer. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). HPLC chromatography was performed on a semi-preparative nucleosil silica column (500x10 mm). All solvents were distilled and purified according to standard procedures prior to use. Purchased starting materials were used without further purification.

All proton and carbon shifts were unambiguously assigned through the use of the following two dimensional NMR techniques: COSY-45 or gradient COSY and HETCOR. The stereochemistry of the IMDA products were resolved by NOESY experiments, and are as shown in the Schemes. When a complete characterization of these compounds was accomplished, common traits could be discerned: in the ^1H spectrum the signals of the olefin multiplet and of the 8- or 9-methyl doublet were shifted up to 0.2 ppm downfield for the *cis* fused product; in the ^{13}C spectrum the signals at the fusion site 5a or 6a were shifted 4.7-7.5 ppm downfield for the *trans* compounds; and a γ-substituent effect[42] was seen between the carbonyl carbon and the 8- or 9-methyl group: the former was shifted 2.3 ppm and the latter 4.8 ppm downfield in the *cis* fused systems.

Synthesis of the dithiolanes 9 and 11, a general procedure:

$TiCl_4$ (5.0 ml, 46 mmol) was dissolved in 10 ml of CH_2Cl_2 at -78 °C under a nitrogen atmosphere. 2-

Methoxy-*N*-carboxymethylpyrrolidine (**6**) or -piperidine (**7**) (46 mmol) in 10 ml of CH_2Cl_2 was added dropwise while maintaining the low temperature. After 45 min vinyl acetate (4.82 g, 56 mmol) was injected *via* a syringe into the solution, which was stirred for another 2 h before it was allowed to reach room temperature; a satutated brine solution was added carefully to the reaction mixture, which was subsequently washed twice with water, dried over $MgSO_4$ and evaporated. The crude aldehyde (*ca* 40 mmol) and ethane-1,2-dithiol (4.75 g, 50 mmol) were dissolved in 20 ml of $CHCl_3$ at -10 °C. $TiCl_4$ (0.58 ml, 5.2 mmol) was added in one portion and the reaction mixture was stirred for about one h before it was quenched with a saturated brine solution. The chloroform layer was then washed once with 2M NaOH and twice with water whereafter it was dried over $MgSO_4$. Evaporation of the solvent and finally chromatography of the product on silica using EtOAc:heptane (1:2) as eluant, yielded the dithiolanes **9** and **11** in 45-69 % yield.

1-Methoxycarbonyl-2-[2-(1',3'-dithiolan)methyl] pyrrolidine **9**: ^{1}HNMR: δ = 4.48 (1H, 7-CH), 3.98 (1H, 2-CH), 3.62 (3H, 10-CH_3), 3.4-3.3 (2H, 5-CH_2), 3.3-3.1 (4H, 8-CH_2), 2.3-1.6 (6H, 3-CH_2, 4-CH_2, 6-CH_2). ^{13}C NMR: δ = 154.94 (C9), 57.08 (C2), 52.29 (C10), 50.66 (CH), 46.25 (C5), 44.51 (C6), 38.55 (C8), 38.20 (C8), 30.98 (C3), 23.75 (C4).
HRMS: found 247.0694; calc. for $C_{10}H_{17}NS_2O_2$: 247.0701. MS: m/z (%) = 247 (M^+, 53), 186 (14), 155 (20), 128 (100), 105 (21), 42 (13). IR(cm^{-1}): ν 1705 (s, C=O).

1-Methoxycarbonyl-2-[2-(1',3'-dithiolan)methyl]piperidine **11**: ^{1}H NMR: δ =4.36 (1H, 8-CH), 4.0 (1H, 6-CH_2), 3.68 (3H, 11-CH_3), 3.3-3.1 (4H, 9-CH_3), 2.81(1H, 6-CH_2), 2.33 (1H, 2-CH), 1.8-1.3 (8H, 3-CH_2, 4-CH_2, 5-CH_2, 7-CH_2). ^{13}C NMR: δ = 156.12 (C10), 52.54 (C11), 50.74 (C7), 40.06 (C2), 39.29 (C6), 38.67 (C9), 37.96 (C9), 29.13 (C3), 25.46 (C5), 19.22 (C4).
HRMS: found 261.0855; calc. for $C_{11}H_{19}NS_2O_2$: 261.0857. MS: m/z (%) = 261 (M^+, 29), 233 (29), 200 (6), 168 (11), 142 (100), 131 (17), 105 (15), 70 (10), 59 (7). IR(cm^{-1}): ν 1700 (s, C=O).

Synthesis of the amines 4 and 5, a general procedure:[26]
The carbamate **9** or **11** (7.0 mmol) was dissolved in 4.2 ml of dry chloroform under an argon atmosphere at 50 °C. Me_3SiI (2.17 ml, 15.2 mmol) was then injected into the vessel dropwise. When all the starting material was consumed, according to TLC, after about 4-5 h, the reaction vessel was placed in a water bath and a mixture of MeOH (4.27g, mmol) and MeONa (0.20g, mmol) was carefully added. The reaction mixture was diluted with 15 ml CH_2Cl_2 and washed with water twice; it was then dried over $MgSO_4$ and evaporated. The crude amines were isolated in 73-76 % yield after chromatography on silica using heptane:EtOAc:Et_3N (60:35:5) as eluant.

2-[2-(1',3'-Dithiolan)methyl]pyrrolidine **4**: ^{1}H NMR: δ = 4.55 (t, 1H, 7-CH, J = 7.5), 3.15 (m, 4H, 9-CH_2), 3.05 (q, 1H, 2-CH, J =7.3), 2.89 (dt, 1H, 5-CH_2-eq, J = -10.6, 6.6), 2.79 (dt, 1H, 5-CH_2-ax, J = -10.6, 6.6), 2.06 (s, 1H, NH), 1.88 (m, 2H, 6-CH_2, J = 7.5, 7.3), 1.84 (m, 1H, 4-CH_2-eq), 1.65 (m, 2H, 3-CH_2), 1.22 (m, 1H, 4-CH_2-ax). ^{13}C NMR: δ = 58.56 (2C), 51.74 (5C), 46.47 (7C), 45.52 (6C), 38.31 (9C), 38.14 (9C); 31.82 (3C), 25.27 (4C).
HRMS: found 189.0644; calc. for $C_8H_{15}NS_2$: 189.0646. MS: m/z (%) = 189 (M^+, 8), 161 (52), 128 (129, 105 (22), 70 (100), 83 (12).

2-[2-(1',3'-Dithiolan)methyl]piperidine **5**: ^{1}H NMR: δ = 4.53 (t, 1H, 8-CH), 3.16 (m, 4H, 9-CH_2), 2.99 (1H, 6-CH_2-eq), 2.60 (1H, 6-CH_2-ax), 2.56 (1H, 2-CH), 1.82 (t, 2H, 7-CH_2), 1.62 (1H, 5-CH_2-eq), 1.52 (1H, 3-CH_2eq), 1.39 (1H, 4-CH_2-eq), 1.27 (1H, 4-CH_2-ax), 1.25 (1H, 5-CH_2-ax), 1.05 (1H, 4-CH_2-ax). ^{13}C NMR: δ = 56.61 (2C), 50.57 (8C), 46.95 (6C), 46.44 (7C), 38.33 (9C), 38.19 (9C), 33.10 (3C), 26.61 (5C), 24.66 (4C). HRMS: found 203.0803; calc. for $C_9H_{17}NS_2$: 203.0802. MS: m/z (%) = 203(M^+, 5), 175(32), 142(5), 105(19), 98(13), 84(100), 56(13).

Synthesis of 12, 13, 14, 16 and 17, a general procedure for the ring-opening reaction:
1[3](1.115 g, 5.00 mmol) was dissolved in toluene (15 ml) together with the amine **2**, **3**, **4** or **5** (20.00 mmol) and placed with a condenser in an oil bath at 100 °C, under a gentle stream of argon. The reaction was completed in 5.5 to 45 hours as determined by GC or TLC. The amines were extracted with 1 % hydrochloric acid and the aqueous phases were neutralized with 2M sodium hydroxide solution and extracted three times with ether. The combined ether phases were dried over $MgSO_4$. Evaporation gave a brownish oil, which was subjected to HPLC chromatography using a mixture of heptane:EtOAc:Et_3N in the proportions 90:5:5 as the eluant.

(2E,4Z)-4-Bromo-1-(2-allylpyrrolidino)-2,4-hexadiene **12**: reaction time 5.5 h, yield: 24 %. ^{1}H NMR: δ = 6.19 (d, 1H, 3-CH, J = 14.9), 6.12 (dt, 1H, 2-CH, J = 14.9, 7.1), 5.97 (q, 1H, 5-CH, J = 6.7), 5.80 (m, 1H, 12-CH, J = 17.0, 10.1), 5.07 (m, 1H, 13-CH-cis, J = 17.0), 5.02 (m, 1H, 13-CH-trans, J = 10.1), 3.57 (dd, 1H, 1-CH_2-eq, J = -13.2, 5.1), 3.09 (m, 1H, 10-CH_2-eq, J = 7.6), 2.88 (dd, 1H, 1-CH_2-ax, J = -13.2, 7.0), 2.41 (m, 1H, 11-CH_2-eq, J = 6.7), 2.35 (m, 1H, 7-CH, J = 7.7, 3.7), 2.15 (m, 1H, 10-CH_2-ax, J = 7.6), 2.05 (m, 1H, 11-CH_2-ax, J = 6.7), 1.87 (d, 3H, 6-CH_3, J =6.7), 1.80 (m, 1H, 8-CH_2-eq), 1.72 (m, 2H, 9-CH_2), 1.56 (m, 1H, 8-CH_2-ax). ^{13}C NMR: δ = 135.88 (12C), 131.23 (2C), 130.98 (3C), 127.96 (5C), 126.11 (4C), 116.30 (13C), 63.46 (7C), 55.34 (1C), 54.26 (10C), 38.57 (11C), 30.09 (8C), 21.96 (9C), 17.18 (6C).
HRMS: found 271.0755; calc. for $C_{13}H_{20}NBr$: 271.0759. MS: m/z (%) = 269/271 (M^+, 16), 228/230 (89), 190 (100), 159/161 (25), 84 (62), 70 (74), 41 (19).

(2E,4Z)-4-Bromo-1-[2-(2-(1',3'-dithiolan)methyl)pyrrolidino]-2,4-hexadiene **16**: reaction time 27 h, yield: 39 %. ^{1}H NMR: δ = 6.17 (d,1H, 3-CH, J = 15.1), 6.08 (m, 1H, 2-CH, J = 15.1, 7.3, 5.2), 5.95 (q, 1H, 5-CH, J = 6.8), 4.43 (dd, 1H, 12-CH, J = 9.0, 5.4), 3.52 (dd, 1H, 1-CH_2, J = -14.3, 5.2), 3.20 (m, 4H, 13-CH_2), 3.05 (m, 1H, 10-CH_2-eq, J = -9.5, 6.6, 3.0), 2.90 (dd, 1H, 1-CH_2, J = -14.3, 7.3), 2.44 (m, 1H, 7-CH), 2.17 (m, 1H, 10-CH_2-ax, J = -9.5), 2.11 (m, 1H, 11-CH_2, J = -13.4, 9.0), 1.98 (m, 1H, 11-CH_2, J = -13.4, 5.2), 1.84 (d, 3H, 6-CH_3, J = 6.8), 1.80 (m, 1H, 8-CH_2-eq), 1.71 (m, 2H, 9-CH_2), 1.50 (m, 1H, 8-CH_2-ax). ^{13}C NMR: δ = 131.18 (3C), 131.02 (2C), 128.05 (5C), 126.11 (4C), 63.54 (7C), 55.71 (12 C), 54.10 (1C), 51.09 (10C), 44.13 (11C), 38.36 (13C), 30.59 (8C), 22.48 (9C), 17.22 (6C).
HRMS: found 347.0376; calc. for $C_{14}H_{22}NS_2Br$: 347.0377. MS: m/z (%) = 347/349 (M^+, 11), 319/321 (15), 268 (13), 228/230 (100), 159/161 (68), 79 (92), 70 (53).

(2E,4Z)-4-Bromo-1-[2-(2-(1',3'-dithiolan)methyl)piperidino]-2,4-hexadiene **17**: reaction time 70 h, yield: 37 %. ^{1}H NMR: δ = 6.17 (d, 1H, 3-CH, J = 14.8), 6.08 (dt, 1H, 2CH, J = 14.8, 6.3), 5.95 (q, 1H, 5-CH, J = 7.1), 4.53 (dd, 1H, 13-CH, J = 8.7, 5.7), 3.39 (d, 1H, 1-CH_2-eq, J = 6.3), 3.21 (m, 4H, 14-CH_2), 3.13 (d, 1H, 1-CH_2-ax, J = 6.3), 2.76 (m, 1H, 11-CH_2-eq), 2.50 (m, 1H, 7-CH, J = 8.1), 2.26 (m, 1H, 11-CH_2-ax), 2.13 (m, 1H, 12-CH_2-eq), 1.94 (dd, 1H, 12-CH_2-ax, J = 8.1, 5.7), 1.85 (d, 3H, 6-CH_3, J = 6.8), 1.74 (m, 1H, 8-CH_2-eq), 1.62 (m, 1H, 9-CH_2-ax), 1.52 (m, 2H, 10-CH_2), 1.39 (m, 1H, 9-CH_2-ax), 1.34 (m, 1H, 8-CH_2-ax).^{13}C

NMR: δ = 131.41 (3C), 130.83 (2C), 127.88 (5C), 126.13 (4C), 59.57 (7C), 54.93 (1C), 51.07 (11C), 50.96 (13C), 40.11 (12C), 38.44 (14C), 38.21 (14C), 29.63 (8C), 24.62 (10C), 22.74 (9C), 17.19 (6C).
HRMS: found 361.0477; calc. for $C_{15}H_{24}NS_2Br$: 361.0533. MS: m/z (%) = 362/364 (MH^+, 100), 282/284 (5), 204 (15), 119 (5).

cis-8-Bromo-6a,9,10,10a-tetrahydro-9-methylbenzo[b]quinolizidine **13**: reaction time 7.5 h, yield: 14 %. ^1H NMR: δ = 5.96 (1H, 7-CH), 2.77 (1H, 6-CH_2-eq), 2.73 (1H, 4-CH_2-eq), 2.45 (1H, 9-CH), 2.39 (1H, 6a-CH), 2.17 (1H, 6-CH_2-ax), 2.09 (1H, 10-CH_2-eq), 1.87 (1H, 10a-CH), 1.85 (1H, 4-CH_2-ax), 1.69 (1H, 1-CH_2-eq), 1.64 (1H, 10-CH_2-ax), 1.62 (1H, 3-CH_2-eq), 1.60 (1H, 11-CH_2-eq), 1.58 (m, 2H, 3-CH_2-ax, 11a-CH), 1.55 (1H, 2-CH_2-eq), 1.48 (1H, 1-CH_2-ax), 1.28 (1H, 11-CH_2-ax), 1.24 (3H, 9-CH_3), 1.22 (1H, 2-CH_2-ax). ^{13}C NMR: δ = 132.44 (7C), 128.42 (8C), 63.07 (11aC), 61.09 (6C), 56.47 (4C), 39.06 (6aC), 35.77 (10C), 35.43 (11C), 35.33 (9C), 32.96 (1C), 32.09 (10aC), 25.49 (3C), 24.43 (2C), 21.61 (9-CH_3).
HRMS: found 283.0941; calc. for $C_{14}H_{22}NBr$: 283.0936. MS: m/z (%) = 283/285 (M^+, 8), 268/270 (7), 204 (100), 98 (25).

trans-8-Bromo-6a,9,10,10a-tetrahydro-9-methylbenzo[b]quinolizidine **14**:reaction time 7.5 h, yield: 11.5 %. ^1H NMR: δ = 5.77 (1H, 7-CH), 2.82 (m, 1H, 4-CH_2-eq, J = -11.3), 2.76 (dd, 1H, J = -10.9, 6-CH_2-eq), 2.51 (m, 1H, 9-CH, J= 7.1), 2.07 (1H, 6a-CH), 2.03 (m, 1H, 4-CH_2-ax, J = -11.3), 1.83 (d, 1H, 6-CH_2-ax, J= -10.9), 1.81 (1H, 11a-CH), 1.72 (1H, 3-CH_2-eq), 1.67 (m, 1H, J = -12.8, 10-CH_2-eq), 1.61 (1H, 3-CH_2-ax), 1.59 (1H, 2-CH_2-eq), 1.57 (2H, 1-CH_2), 1.51 (m, 1H, 10-CH_2-ax, J= -12.8), 1.48 (1H, 10a-CH), 1.29 (1H, 11-CH_2-eq), 1.25 (1H, 2-CH_2-ax), 1.20 (d, 3H, 9-CH_3, J = 7.1), 1.08 (1H, 11-CH_2-ax). ^{13}C NMR: δ = 130.52 (7C), 130.34 (8C), 62.96 (11aC), 60.58 (6C), 56.16 (4C), 43.72 (6aC), 39.16 (10aC), 38.56 (9C), 36.98 (10C), 33.55 (11C), 33.13 (1C), 25.85 (3C), 24.53 (2C), 21.61 (9-CH_3). HRMS: found 283.0938; calc. for $C_{14}H_{22}NBr$: 283.0936. MS: m/z (%) = 283/285 (M^+, 10), 204 (100).

Synthesis of 18 and 19, a general procedure for the Wittig reaction:
16 or **17** (0.29 mmol) was dissolved in 1.44 ml THF. HgO (124 mg, 0.57 mmol) was added and then 0.2 ml of 50 % aqueous HBF_4. The reaction mixture was stirred vigorously and all the starting material was consumed in less than 30 min; 2 ml 10 %-NaOH was then added to the reaction mixture, which was further diluted with 5 ml CH_2Cl_2. The phases were separated and the organic layer was washed with 10 % KI, 10 % NaOH and water before it was dried over $MgSO_4$ and finally evaporated *in vacuo*. The crude aldehyde was dissolved in 5 ml of CH_2Cl_2 and was reacted directly with Ph_3P=CHCOOEt (120mg, 0.3457 mmol) at ambient temperature for 2 h to give 14 or 16 in 28-29 % overall yield, after HPLC work-up with heptane:EtOAc:Et_3N (90:5:5) as eluant.

(2E,4Z)-4-Bromo-1-[2-(ethylbut-2-enoyl)pyrrolidino]-2,4-hexadiene **18**:13 (0.29 mmol) gave 14 (27.8 mg, 81.2μmol) in 28 % yield. ^1H NMR: δ = 6.92 (dt, 1H, 12-CH, J = 15.6, 7.2), 6.20 (d, 1H, 3-CH, J = 14.7), 6.09 (dd, 1H, 2-CH, J = 14.7, 7.1, 5.3), 5.98 (q, 1H, 5-CH, J = 6.7), 5.83 (d, 1H, 13-CH, J = 15.6), 4.17 (q, 2H, 15-CH_2, J = 7.1), 3.52 (dd, 1H, 1-CH_2-eq, J = -13.8, 5.2), 3.10 (t, 1H, 10-CH_2-eq, J = -8.3), 2.96 (dd, 1H, 1-CH_2-ax, J = -13.8, 7.1), 2.61 (m, 1H, 11-CH_2-eq, J = -9.2, 7.2), 2.49 (m, 1H, 7-CH), 2.23 (m, 1H, 11-CH_2-ax, J = -9.2), 2.18 (m, 1H, 10-CH_2-ax, J = -8.3), 1.91 (m, 1H, 8-CH_2-eq), 1.86 (d, 3H, 6-CH_3, J = 6.7), 1.82-1.66 (m, 2H, 9-CH_2), 1.52 (m, 1H, 8-CH_2-ax), 1.28 (t, 3H, 16-CH_3, J = 7.1). ^{13}C NMR: δ = 166.46 (14C), 146.18 (12C), 131.45 (3C), 130.45 (2C), 128.45 (5C), 125.91 (4C), 123.01 (13C), 62.66 (7C), 55.22 (1C), 54.09

(10C), 37.08 (11C), 30.33 (8C), 22.14 (9C), 17.21 (6C), 14.28 (16C). IR(cm^{-1}): ν 1720 (s, C=O).
HRMS: found 340.0919 (-H); calc. for $C_{16}H_{24}NO_2Br$: 341.0990. MS: m/z (%) = 341/343 (M^+, 12), 262 (100), 84 (55).

(2E,4Z)-4-Bromo-1-[2-(ethyl-but-2-enoyl)piperidino]-2,4-hexadiene **19**: 15 (0.29 mmol) gave 16 (29.8 mg, 83.6 μmol) in 29 % yield. ^{1}H NMR: δ = 6.95 (dt, 1H, 13-CH, J = 15.6, 6.8), 6.18 (d, 1H, 3-CH, J = 15.0), 6.10 (dd, 1H, 2-CH, J = 15.0, 6.3), 5.98 (q, 1H, 5-CH, J = 6.7), 5.83 (d, 1H, 14-CH, J = 15.6), 4.18 (q, 2H, 16-CH_2, J = 7.1), 3.42 (dd, 1H, 1-CH_2-eq, J = -15.0, 6.3), 3.11 (dd, 1H, 11-CH_2-eq, J = 6.8), 2.96 (dd, 1H, 1-CH_2-ax, J = -15.0, 6.3), 2.49 (m, 1H, 7-CH), 2.43 (m, 1H, 12-CH_2-eq), 2.20 (m, 1H, 12-CH_2-ax), 2.18 (dd, 1H, 11-CH_2-ax, J = 6.8), 1.88 (d, 3H, 6-CH_3, J = 6.7), 1.80-1.30 (6H, 8-CH_2, 9-CH_2, 10-CH_2), 1.31 (t, 3H, 16-CH_3, J = 7.1). ^{13}C NMR: δ = 166.46 (15C), 146.47 (13C), 131.64 (3C), 130.02 (2C), 128.19 (5C), 125.98 (4C), 123.10 (14C), 59.06 (7C), 55.36 (1C), 52.01 (11C), 34.27 (12C), 30.84 (8C), 25.58 (10C), 23.13 (9C), 17.18 (6C), 14.27 (17C). IR(cm^{-1}): ν 1720 (s, C=O).
HRMS: found 354.1068 (-H); calc. for $C_{17}H_{26}NO_2Br$: 355.1147.

Synthesis of 20, 21, 22, 23, 24 and 25, a general procedure for the thermal IMDA reaction:
Around 0.50 mmol of the triene was dissolved in 50 ml toluene in a 100 ml glass ampoule, which repeatedly, *i.e.* three times, was evacuated and flushed with argon before it was sealed, placed in a steel bomb in an oven at 150 °C or 100 °C for the time indicated below. The toluene was evaporated *in vacuo*; the product mixture was then dissolved in diethyl ether (2 ml) and filtered through a cotton crammed pasteur pipette. Separation of the *cis* and *trans* fused products was achieved after HPLC chromatography using a mixture of heptane:EtOAc:Et_3N in the proportions 95:5:5 as the eluant.

12 (106 mg, 0.392 mmol) gave a mixture of **20** and **21** (96.3 mg, 0.356 mmol) in a ratio of 55:45 in 91 % yield; reaction temperature 150 °C, reaction time 26 h.
cis-7-Bromo-5a, 8, 9, 9a-tetrahydro-8-methylbenzo[b]indolizidine **20**: ^{1}H NMR: δ = 5.93 (b, 1H, 6-CH), 3.02 (dd, 1H, 5-CH_2-eq, J = -11.4, 2.0), 2.97 (dd, 1H, 3-CH_2-eq, J = -8.5, 2.5), 2.46 (m, 1H, 8-CH, J = 7.4), 2.43 (m, 1H, 5a-CH, J = 3.9, 2.0), 2.19 (dd, 1H, 5-CH_2-ax, J = -11.4, 3.9), 2.15 (m, 1H, 9-CH_2-eq), 2.03 (m, 1H, 3-CH_2-ax, J = -8.5), 1.86 (m, 1H, 9a-CH), 1.80 (m, 1H, 2-CH_2-eq), 1.70 (m, 1H, 1-CH_2-eq), 1.65 (m, 1H, 10a-CH), 1.60 (m, 2H, 2-CH_2-ax, 9 -CH_2-ax), 1.57 (m, 2H, 10-CH_2), 1.37 (m, 1H, 1-CH_2-ax), 1.25 (d, 3H, 8-CH_3, J = 7.4). ^{13}C NMR: δ = 132.43 (6C), 128.59 (7C), 64.99 (10aC), 57.62 (5C), 54.29 (3C), 39.11 (5aC), 35.81 (9C), 35.46 (8C), 33.54 (10C), 32.61 (9aC), 30.52 (1C), 21.53 (8-CH_3), 21.16 (2C).
HRMS: found 271.0758; calc. for $C_{13}H_{20}NBr$: 271.0759. MS: m/z (%) = 269/271 (M^+, 14), 254/256 (9), 190 (100), 84 (51).
trans-7-Bromo-5a, 8, 9, 9a-tetrahydro-8-methylbenzo[b]indolizidine **21**: ^{1}H NMR: δ = 5.82 (b, 1H, 6-CH), 3.07 (m, 1H, 5-CH_2-eq), 3.04 (m, 1H, 3-CH_2-eq), 2.54 (m, 1H, 8-CH, J = 7.1), 2.13 (m, 1H, 3-CH_2-ax), 2.10 (m, 1H, 5a-CH), 1.93 (m, 1H, 10a-CH), 1.84 (m, 1H, 1-CH_2-eq), 1.82 (m, 1H, 5-CH_2-ax), 1.74 (m, 1H, 9-CH_2-eq), 1.67 (m, 2H, 2-CH_2), 1.57 (m, 1H, 9 -CH_2-ax), 1.40 (m, 1H, 1-CH_2-ax), 1.32 (m, 1H, 9a-CH), 1.21 (d, 3H, 8-CH_3, J = 7.1), 1.03 (m, 1H, 10-CH_2-ax). ^{13}C NMR: δ = 130.74 (6C), 130.18 (7C), 64.56 (10aC), 56.60 (5C), 53.40 (3C), 43.99 (5aC), 38.73 (8C), 37.29 (9C), 36.57 (10C), 33.40 (9aC), 30.04 (1C), 21.19 (2C), 20.68 (8-CH_3).
HRMS: found 271.0760; calc. for $C_{13}H_{20}NBr$: 271.0759. MS: m/z (%) = 269/271 (M^+, 18), 254/256 (7), 190 (82), 84 (100), 41 (13).

18 (29.5 mg, 86.2 μmol) gave a mixture of **22** and **23** (29 mg, 84.7 μmol) in a ratio of 73:27 in nearly quantitative yield (98.3 %); reaction time 17 h.

cis-7-Bromo-9-carboxyethyl-5a, 8, 9, 9a-tetrahydro-8-methylbenzo[b]indolizidine **22**: ^{1}H NMR: δ = 5.95 (1H, 6-CH), 4.15 (2H, 12-CH_2, J = 7.2), 3.00 (1H, 5-CH_2-eq), 2.96 (1H, 3-CH_2-eq), 2.87 (m, 1H, 8-CH, J = 7.5), 2.56 (1H, 9-CH), 2.47 (1H, 5a-CH), 2.25 (1H, 5-CH_2-ax), 2.22 (1H, 9a-CH), 1.87 (3H, 1-CH_2-eq, 2-CH_2-eq, 3-CH_2-ax), 1.70 (m, 1H, 1-CH_2-eq), 1.67 (3H, 2-CH_2-ax, 10-CH_2-eq, 10a-CH), 1.55 (1H, 10-CH_2-ax), 1.40 (1H, 1-CH_2-ax), 1.31 (d, 3H, 8-CH_3, J = 7.5), 1.25 (t, 3H, 13-CH_3, J = 7.2). ^{13}C NMR: δ = 174.26 (11C), 131.49 (6C), 126.57 (7C), 64.44 (10aC), 60.86 (12C), 56.84 (9C), 54.13 (5C), 51.54 (3C), 36.84 (8C), 35.76 (5aC), 33.38 (10C), 34.77 (9aC), 30.45 (1C), 21.26 (2C), 20.72 (8-CH_3), 14.25 (13C). IR(cm^{-1}): ν 1725 (s, C=O).

HRMS: found 341.0962; calc. for $C_{16}H_{24}NO_2Br$: 341.0990. MS: m/z (%) = 341/342 (M^+, 21), 262 (100), 84 (58).

trans-7-Bromo-9-carboxyethyl-5a,8,9, 9a-tetrahydro-8-methylbenzo[b]indolizidine **23**: ^{1}H NMR: δ = 5.83 (1H, 6-CH), 4.15 (2H, 12-CH_2, J = 7.1), 3.09 (1H, 5-CH_2-eq), 3.03 (1H, 3-CH_2-eq), 2.82 (m, 1H, 8-CH, J= 6.9), 2.76 (1H, 9-CH), 2.22 (1H, 10-CH_2-eq), 2.18 (1H, 5a-CH), 2.12 (1H, 3-CH_2-ax), 1.97 (1H, 10a-CH), 1.87 (1H, 5-CH_2-ax), 1.82 (2H, 2-CH_2), 1.71 (1H, 1-CH_2-eq), 1.57 (1H, 9a-CH), 1.38 (1H, 1-CH_2-ax), 1.12 (d, 3H, 8-CH_3, J= 6.9), 1.27 (t, 3H, 13-CH_3, J = 7.1), 0.93 (1H, 10-CH_2-ax). ^{13}C NMR: δ = 171.94 (11C), 130.18 (6C), 127.72 (7C), 64.61 (10aC), 60.35 (12C), 56.39 (5C), 53.17 (3C), 49.53 (9C), 43.27 (5aC), 40.72 (8C), 34.52 (9aC), 33.03 (10C), 29.70 (1C), 21.16 (2C), 16.03 (8-CH_3), 14.26 (13C). IR(cm^{-1}): ν 1725 (s, C=O).

HRMS: found 271.0760; calc. for $C_{16}H_{24}NO_2Br$: 341.0990. MS: m/z (%) = 341/343 (M^+, 10), 262 (100), 84 (30).

19 (49.5 mg, 0.1389 mmol) gave a mixture of **24** and **25** (48.2 mg, 0.1353 mmol) in a ratio of 70:30 in 97 % yield; reaction temperature 100 °C, reaction time 17 h.

cis-8-Bromo-10-carboxyethyl-6a,9,10,10a-tetrahydro-9-methylbenzo[b]quinolizidine **24**: ^{1}H NMR: δ = 5.98 (1H, 7-CH), 4.14 (q, 2H, 13-CH_2, J = 7.1), 2.80 (1H, 6-CH_2-eq), 2.72 (1H, 4-CH_2-eq), 2.87 (1H, 9-CH), 2.56 (1H, 10-CH), 2.42 (1H, 6a-CH), 2.24 (1H, 10a-CH), 2.19 (1H, 6-CH_2-ax), 1.89 (1H, 4-CH_2-ax), 1.68 (1H, 3-CH_2-eq), 1.66 (1H, 1-CH_2-eq), 1.63 (2H, 1-CH_2-ax, 11a-CH), 1.52 (m, 1H, 3-CH_2-ax), 1.51 (m, 1H, 2-CH_2-eq), 1.32 (3H, 9-CH_3), 1.29 (1H, 11-CH_2-eq), 1.27 (1H, 2-CH_2-ax), 1.26 (t, 3H, 14-CH_3, J = 7.1), 0.94 (1H, 11-CH_2-ax).^{13}C NMR: δ = 174.33 (12C), 131.74 (7C), 126.10 (8C), 62.92 (11aC), 60.82 (13C), 60.61 (6C), 56.30 (4C), 51.26 (10C), 36.68 (9C), 35.81 (6aC), 35.51 (1C), 34.62 (10aC), 32.82 (11C), 25.43 (3C), 24.34 (2C), 20.90 (9-CH_3), 14.25 (14C). IR(cm^{-1}): ν 1720 (s, C=O). HRMS: found 354.1067 (-H); calc. for $C_{17}H_{26}NO_2Br$: 355.1147. MS: m/z (%) = 355/357 (M^+, 21), 340/342 (5), 310/312 (6), 276 (100), 148 (18), 98 (35).

trans-8-Bromo-10-carboxyethyl-6a,9,10,10a-tetrahydro-9-methylbenzo[b]quinolizidine **25**: ^{1}H NMR: δ = 5.78 (1H, 7-CH), 4.14 (q, 2H, 13-CH_2, J = 7.0), 2.80 (1H, 6-CH_2-eq), 2.82 (1H, 4-CH_2-eq), 2.74 (1H, 9-CH), 2.71 (1H, 10-CH), 2.18 (1H, 6a-CH), 2.04 (1H, 4-CH_2-ax), 1.94 (1H, 11-CH_2-eq), 1.88 (1H, 11a-CH), 1.85 (1H, 6-CH_2-ax), 1.70 (m, 1H, 2-CH_2-eq), 1.60 (2H, 3-CH_2-eq), 1.58 (1H, 1-CH_2-eq), 1.55 (1H, 10a-CH), 1.25 (t, 3H, 14-CH_3, J = 7.1), 1.24 (2H, 1-CH_2-ax, 2-CH_2-ax), 1.10 (3H, 9-CH_3), 0.94 (1H, 11-CH_2-ax).^{13}C NMR: δ = 171.98 (12C), 130.21 (7C), 127.74 (8C), 62.78 (11aC), 60.30 (13C), 60.39 (6C), 55.99 (4C), 49.46

(10C), 40.53 (9C), 43.25 (6aC), 32.96 (1C), 34.14 (10aC), 36.09 (11C), 25.76 (3C), 24.45 (2C), 16.05 (9-CH_3), 14.25 (14C). IR(cm^{-1}): ν 1720 (s, C=O).
HRMS: found 354.1067 (-H); calc. for $C_{17}H_{26}NO_2Br$: 355.1147. MS: m/z (%) = 355/357 (M^+, 10), 276 (100), 98 (23).

Synthesis of 22, 23, 24 and 25, a procedure for the $TiCl_4$ catalyzed IMDA reaction:
The trienes **18** and**19** were each dissolved in dry CH_2Cl_2 (distilled over P_2O_5) under argon to form a 37.72 mM solution with respect to both the triene and the dodecane, which was used as internal standard. A fresh 75.44 mM $TiCl_4$ solution in dry CH_2Cl_2 was then prepared, also under argon. Equivalent volumes, usually around 200 µl, of the reagent solutions were combined and stirred gently under argon at ambient temperature for 18 h. Two ml of chloroform was added to the reaction mixture, which was then washed three times with 1% HCl and once with a 10 % $NaHCO_3$ solution; the organic phase was then dried over $MgSO_4$, filtered and analysed on a capillary GC. The solvents were removed by a gentle stream of argon and the products were dissolved in $CDCl_3$. Their proton spectra were recorded and found to be identical with those listed above for **22**, **23**, **24** and **25**. The conversion was total and the yields were quantitative for both the trienes. The *cis*:*trans* ratios spanned from 7:93 to 5:95.

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