A Short Intramolecular Diels–Alder Route to Himbacine Derivatives

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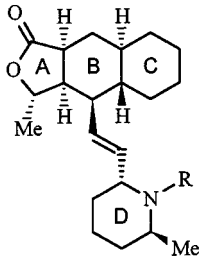
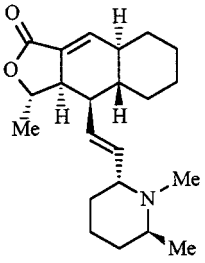
The intramolecular cycloaddition of **5** yields the unsaturated lactones **17a**, **17b**, and **17c** as three major isomeric adducts. These were further reduced to the corresponding derivatives **21a**, **21b**, and **21c**, which are intermediates for the synthesis of (+)-himbacine and stereoisomers thereof. Precursor **5** was obtained in a short convergent way using Sonogashira and Stille coupling reactions as the main C–C bond construction reactions.

Introduction

Himbacine (**1**), himbeline (**2**), himgravine (**3**), and a few related piperidine alkaloids were isolated forty-five years ago from the bark of *Galbulimima baccata*.[1] Synthetic interest in this series arose when it was discovered that himbacine is a potent muscarinic receptor antagonist with selectivity for the M_2 receptor.[2] Since the blocking of presynaptic muscarinic receptors may contribute to the treatment of diseases in which the central cholinergic system degenerates,[3] the development of highly selective and potent M_2 antagonists constitutes a timely challenge.[4] It is also evident that substances possessing some structural analogy with himbacine constitute prime candidates in this context. So far the few studies that have been conducted to establish structure–activity relationships in this area, have shown that the deletion of substantial parts of the skeleton and/or functionality of the natural derivative results in loss of affinity and/or selectivity.[5–7] Thus, we became interested in the synthesis of intact stereoisomers of (+)-himbacine focussing on the stereogenic centres in the tricyclic system of the molecule. Here we wish to describe a short convergent approach leading to three isomeric series, including the natural one, that is based on an intramolecular Diels–Alder process.



1 R = Me
2 R = H



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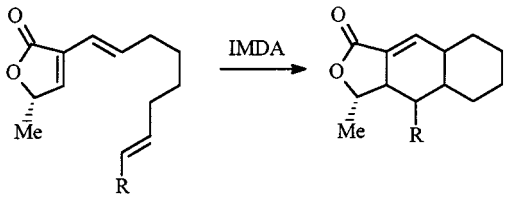
Results and Discussion

The Intramolecular Diels–Alder Strategy

Several features of the structure of himbacine (**1**) make it an attractive and challenging target for total synthesis.[8–10] Its tetracyclic skeleton reveals an ABC-ring part, consisting of a *trans*-fused perhydronaphthalene to which a γ-lactone is *cis*-fused. This part is connected, by an (*E*)-double bond, to an *N*-methyl 2,6-*trans*-disubstituted piperidine D-ring. Furthermore, six contiguous stereocentres are present in the ABC-ring system.

It is symptomatic of the power of the Diels–Alder reaction in terms of cyclic skeleton construction involving stereochemical constraints, that among the five reported strategies towards himbacine,[8–12] all involve a Diels–Alder reaction as the key step for the synthesis of the ABC-ring part, four with an intramolecular version (IMDA)[8,9,11,12] and, among these four, three approaches deal with the bond construction indicated in Equation (1).[8,11,12] Furthermore, the latter approach leads to the unsaturated ring system as is present in the structure of himgravine (**3**), the selective reduction of which to himbacine (**1**) has been described before.[13]



(1)

In the context of the IMDA approach shown in Equation (1) two aspects to be addressed remain: (1) The choice of the nature of R, and (2) the stereochemical outcome of

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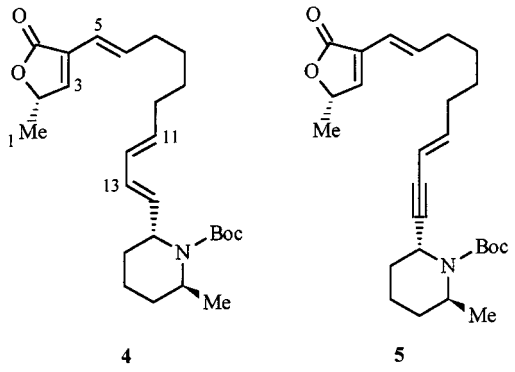
the cycloaddition. In the syntheses reported so far, the process has involved activated dienophiles with R = CHO, COSPh;[8,11] the latter functions were then used in the further synthetic sequence for the attachment of the D-ring. In the present work we wish to focus on the cycloaddition reaction of advanced intermediates, such as **4** and **5**, in which the piperidine D-ring is already present.[14]



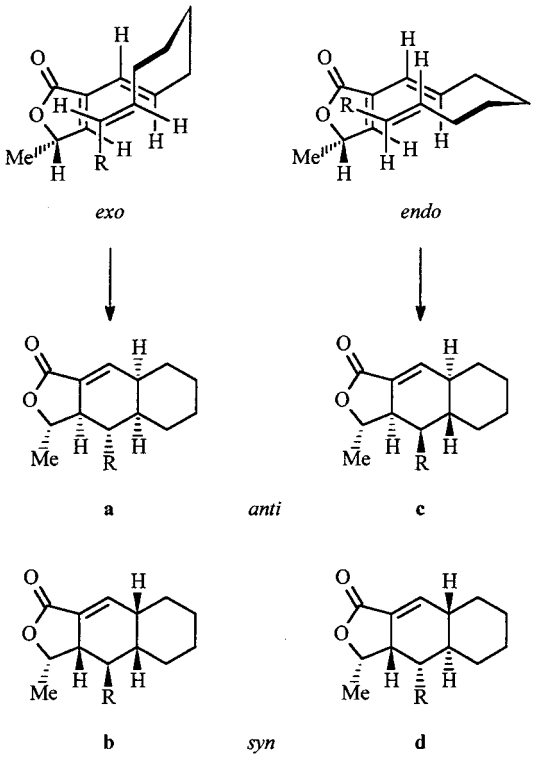
4 **5**

Whereas an efficient route to tetraene **4** was developed,[15] its thermal cycloaddition at 185 °C led to a complex mixture in which a major portion consisted of adducts originating from the reaction of the conjugated 5,6-double bond as the dienophile with the 11,13-diene. Obviously, this competitive pathway is not possible in the case of enyne **5**, the substrate on which we will further concentrate.

The stereochemical outcome of the IMDA process is determined by (1) the *exo*- or *endo*-mode of addition, and by (2) the *anti*- or *syn*-approach of the dienophile relative to the orientation of the butenolide methyl group (Figure 1). Whereas the *anti*-approach should be preferred on the basis of steric considerations, thus favouring the **a**- and **c**-configurations over the **b**- and **d**-configurations, discrimination between the *exo*- and *endo*-modes of addition is less obvious. In many cases the cycloaddition of (*E*,*E*,*E*)-1,3,9-decatrienes occurs with low stereoselectivity The use of Lewis acid catalysis often enhances the *endo*-selectivity.[16] This general trend has also been observed in the cycloaddition reaction of a series of substrates related to **5** (Table 1). Under thermal conditions, substrate **6** involving an unactivated dienophile and a voluminous R-group leads preferentially to the *exo*,*anti* adduct **a**,[8b] whereas the unsaturated ester **7** yields a 1:1 mixture of *anti* adducts **a** and **c**.[8b,11b] Under Lewis acid activation the unsaturated thioester **8** gave almost exclusively the *endo*,*anti* adduct **c**.[8] On the other hand, thermal reaction of the unsaturated aldehyde **9** involving a small R-group leads to a mixture where *syn* adduct **b** and **d** formation is also observed.[11,12]

A Short Convergent Synthesis of Precursor 5

The convergent approach that was elaborated for the synthesis of **5** is shown in Scheme 1. Assembly of the skeleton proceeds by C−C bond formations at C4−C5 and at C12−C13, involving the readily available intermediates **10**, **11**, and **12**.



exo *endo*

a *anti* **c**

b *syn* **d**

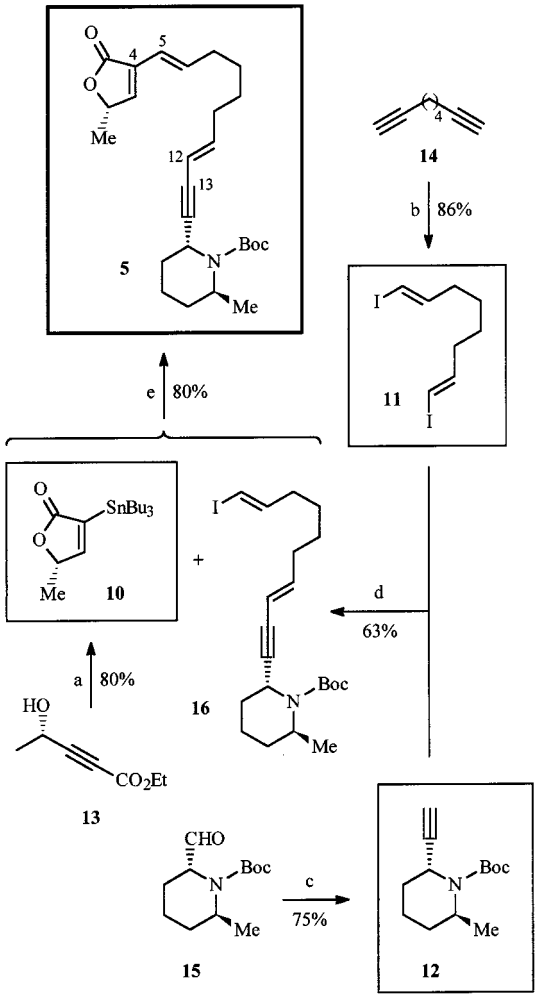
Figure 1. Stereochemical outcome of the IMDA shown in Equation (1) including adduct stereodesignations **a**, **b**, **c**, and **d**

Table 1. Intramolecular cycloaddition of **6**−**9**

Substrate [see Equation (1)]	Reaction Conditions *T*[°C]; time [h]	Yield [%]	Ratio[a] **a/b/c/d**
6, R = $CH_2OTBDMS$	210; 18	82[b]	4:0:1:0
7, R = CO_2Et	110; 24	58[b]	1:0:1:0
	170; 24	85[c]	1:0:1:0
8, R = COSPh	SiO_2-Et_2AlCl	75[b]	1:0:20:0
9, R = CHO	170; 24	85[c]	6:8:10:1
	$Me_3SiOSO_2CF_3$	20[d]	3 isomers

[a] Stereochemical designations according to Figure 1. − [b] Reference [8b];. − [c] Reference [11b];. − [d] Reference [12]; the corresponding acetal led to the almost exclusive formation of **c** (53% yield) under the same conditions.

The recently described stannylfuranone **10**[17] was obtained in enantiomerically pure form via palladium(0) catalysed *syn*-addition of tributyltin hydride to the known ethyl (4*S*)-hydroxypent-2-ynoate (**13**).[18] As well as the desired stannane derivative **10** (80% yield) the regio-isomeric (5*S*)-methyl-4-tributylstannyl-2(5*H*)-furanone was also obtained (10% yield); both were readily separated by flash chromatography on silica. Enantiomerically pure ester **13**[19] is readily prepared from (*S*)-3-butyn-2-ol[20] in 75% overall yield by a sequence involving: (i) protection of the hydroxy group as *tert*-butyldimethylsilyl ether [*tert*-butyldimethylsilyl chloride, triethyl amine, and 4-(dimethylamino)pyridine in tetrahydrofuran]; (ii) introduction of the ethoxycarbonyl group (*n*-butyllithium, ethyl chloroformate in tetrahydrofuran at −78 °C; (iii) deprotection (aqueous acetic acid-tetrahydrofuran at 60 °C).[21]



Scheme 1. Synthesis of Diels–Alder precursor **5**. Reagents and conditions: a, $(n\text{Bu})_3\text{SnH}$, Pd(PPh)_4, THF; b, $(i\text{Bu})_2\text{AlH}$, hexane, 50 °C, followed by I_2, THF, −50 °C to 25 °C; c, Me_3SiCHN_2, $\text{LiN}(i\text{Pr})_2$, THF; d, $\text{Pd(PPh}_3)_4$, piperidine; e, CuCl, DMF, 60 °C

The preparation of (1*E*,7*E*)-1,8-diiodooctadiene (**11**) involved the stereoselective bis-*syn*-hydroalumination[22] of the commercially available 1,7-octadiyne (**14**) with diisobutylaluminum hydride (hexane, 50 °C), followed by iodination (iodine, tetrahydrofuran, −50 °C to room temperature; 86% yield).[23]

Finally, the required alkyne **12** was obtained from the known aldehyde **15** according to Shiori's method,[24] which involves reaction of **15** with deprotonated (trimethylsilyl)diazomethane (lithium diisopropylamide, tetrahydrofuran; 75% yield). It is worthwhile noting that this reaction occurs without isomerisation to the more stable *cis*-2,4-disubstituted piperidine derivative.[25] Aldehyde **15** can be obtained following different routes,[8b][9b][11b] the most convenient of which involves the Beak formylation[26] of (*S*)-*N*-Boc-2-methylpiperidine as described by Chackalamannil (*sec*-butyllithium, tetramethylethylenediamine, diethyl ether at −78 °C, followed by reaction with dimethylformamide).[9] Commercially available 2-methylpiperidine is resolved using L-tartaric acid, with the tartrate salt being directly converted into the *N*-Boc-protected derivative (di-*tert*-butyl dicarbonate, 10% sodium hydroxide).[27]

Two consecutive coupling processes led to **5**: (i) The Sonogashira coupling [tetrakis(triphenylphosphane)palladium(0), piperidine] between iodoalkene **11** and alkyne **12** proceeded in fair yield when using a twofold excess of iodide in order to suppress the formation of bis-coupled product (63% yield of **16**);[28] (ii) the Stille coupling between stannylfuranone **10** and iodoalkene **16** was performed in dimethylformamide at 60 °C using 2.75 equiv. of copper(I) chloride, yielding 80% of the desired product **5** (15 mM scale).[29]

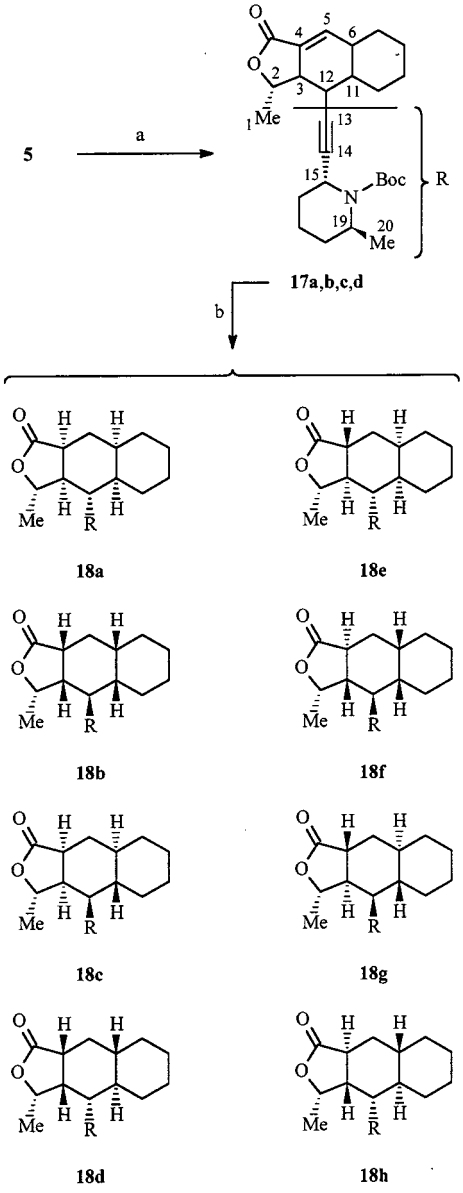
The Intramolecular Diels–Alder Reaction of 5 and Synthesis of the Lactones 18

The thermal cycloaddition of **5** (toluene, reflux, 3 days) led to an inseparable mixture of four adducts **17** (yield 80%; ratio 10:7:5:1 by ^{1}H NMR). Chromatographic separation of the three major isomers was accomplished after reduction of the conjugated double bond in **17** with magnesium in methanol,[30] giving lactones **18a**, **18b**, and **18c** in 40%, 21%, and 31% yield, respectively (Scheme 2). Whereas a preliminary identification of stereoisomers **18a**, **18b**, and **18c** is possible on the basis of ^{1}H NMR spectroscopic data (Table 2), the final structural assignment of the three major isomeric series was established at a later stage (vide infra). Minor amounts of a fourth (2%), fifth (2%), and sixth lactone (2%) were also obtained to which structures **18d**, **18e**, and **18f**, respectively, were tentatively assigned (Table 2).

The stereochemical outcome of this two-step sequence is determined by the cycloaddition (stereocentres 3, 6, 11, 12) and by the subsequent magnesium in methanol reduction (stereocentre 4).[31] The preferred formation of *anti* adducts **a** and **c**, with the *exo*-isomer **a** as major isomer, is in line with the previous discussion (Table 1). On the basis of steric considerations the third major isomer in the cycloaddition is expected to be the *syn*,*exo* adduct **b**. Presumably the stereochemical outcome of the conjugate reduction of adducts **17a**, **17b**, and **17c** is kinetically determined at the stage of the proton addition to the intermediate enolate anion; this is expected to occur from the least hindered convex side of the molecule (Figure 2), and to lead to the *cis*-fused lactones **18a**, **18b**, and **18c**. Force field calculations[32] indicate a small steric energy difference between the *cis*- and *trans*-fused lactones **18a** and **18e** (2.1 kJ mol^{-1} in favour of **18e**), **18b** and **18f** (3.1 kJ mol^{-1} in favour of **18f**), and a large energy difference between **18c** and **18g** (14.2 kJ mol^{-1} in favour of **18c**), **18d** and **18h** (19.1 kJ mol^{-1} in favour of **18d**). In this context it is not surprising to isolate minor amounts of **18e** and of **18f** which can result from some equilibration of **18a** and of **18b**, respectively.

The Synthesis of Lactones 21

The further conversion of lactones **18a**, **18b**, and **18c** to himbacine-type derivatives requires the stereoselective reduction of the triple bond to the corresponding (*E*)-alkene. The following reaction sequence was developed for that



Scheme 2. Synthesis of the stereoisomeric lactones **18a**, **18b**, and **18c**. Reagents and conditions: a, toluene, 110 °C, 3 days; b, Mg, MeOH

purpose as is shown for **21c** (Scheme 3): (i) Reduction of the lactone **18c** followed by immediate conversion into the corresponding acetal (1 M diisobutylaluminum hydride in hexane, toluene, −78 °C, followed by boron trifluoride diethyl etherate in methanol/dichloromethane; yield of isolated **19c**: 96%); (ii) stereoselective reduction of alkyne **19c** under dissolving metal conditions (lithium in liquid ammonia, *tert*-butyl alcohol; yield of **20c**: 96%); (iii) Jones oxidation of acetal **20c** to the corresponding lactone **21c** (isolated yield: 99%). The same reaction sequence led to **21b** when starting from **18b** (overall yield: 89%). Application of this sequence to **18a** also resulted in an excellent yield of **21a** (92%); in this series **19a** was obtained as a stereoisomeric mixture of acetals (ratio 7:1). Although the configuration at the acetal carbon in **19** and **20** is of no further concern

Table 2. Vicinal coupling constant values related to H3 in lactones **18**

Compound	J(H2,H3)[a]	J(H3,H4)[a]	J(H3,H12)[a]
	Calculated [Hz][b]		
18a	2.9	6.8	9.9
18b	5.1	6.4	11.6
18c	10.0	6.8	4.9
18d	7.1	7.7	5.9
18e	10.3	13.0	12.5
18f	6.4	13.0	12.5
18g	10.3	12.7	6.2
18h	6.7	12.5	5.0
	Experimental [Hz][c]		
18a	0.0	7.5	11.4
18b	4.7	7.2	11.2
18c[e]	10.2	6.7	5.4
18d[e]	9.9	6.5	—[d]
18e	9.8	12.9	11.0
18f	6.7	12.3	11.4

[a] Atom numbering as indicated in **17** (Scheme 2). — [b] MacroModel, see reference [32]. — [c] 500 MHz, $CDCl_3$, HH-COSY. — [d] Could not been assigned. — [e] C_6D_6 as solvent.

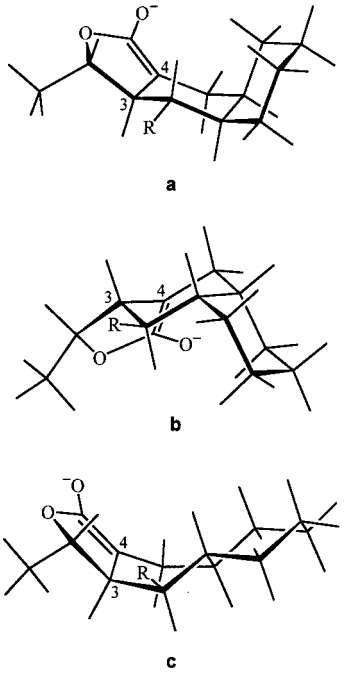
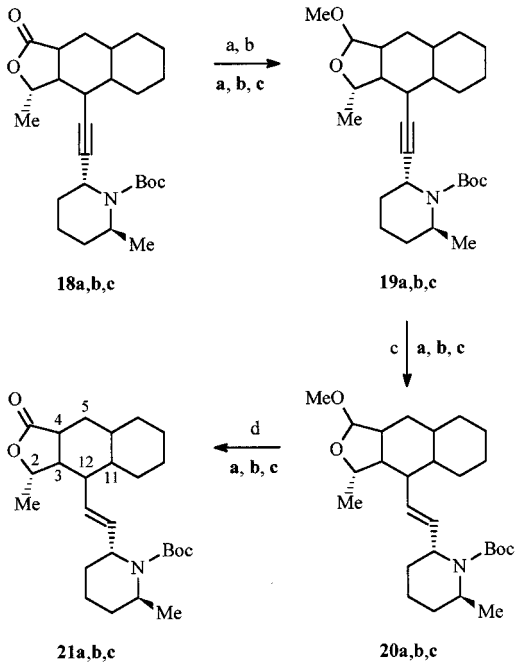


Figure 2. Global minimum energy conformations of the intermediate enolate anions expected upon conjugate reduction of **17a**, **17b**, and **17c** (R = 1-propenyl), as calculated by MacroModel[32]

here, the methoxy group is expected to be oriented along the convex side of the *cis*-fused AB-ring system, hence α-oriented in the **a**- and **c**-series and β-oriented in the **b**-series.[33]

The relevant ^{1}H NMR spectroscopic data of **21a**, **21b**, and **21c**, are shown in Table 3. Comparison of the data with those obtained by molecular modelling is very instructive



Scheme 3. Synthesis of the stereoisomeric lactones **21a**, **21b**, and **21c**. Reagents and conditions: a, $(i\text{Bu})_2\text{AlH}$, toluene, −78 °C; b, Et_2O-BF_3, MeOH, CH_2Cl_2; c, Li, liquid NH_3, *t*BuOH; d, CrO_3-H_2SO_4, acetone. Stereochemical designations as shown in Scheme 2

and corroborates the preliminary structural assignments. Final structural confirmation in the **a**-series was obtained via X-ray diffraction analysis of lactone **21a**. A perspective view of the X-ray structure is shown in Figure 3. It is also interesting to note that the twist-conformation adopted by the *N*-Boc protected piperidine D-ring is almost identical with the one of a similar D-ring intermediate reported by Chackalamannil.[9b] On the other hand, in the calculated global minimum energy conformation of **21a**,[32] which is 5 kJ mol^{-1} more stable than the X-ray geometry, the D-ring adopts a chair conformation.

Table 3. Relevant NMR spectroscopic data of H2, H3, H4, H11, and H12 in lactones **21a**, **21b**, and **21c**

Protons[c]	*J*[Hz] experimental[a] (calculated)[b] 21a	21b	21c
2, 3	0 (1.7)	4.8 (5.2)	10.3 (9.9)
3, 4	7.6 (6.7)	7.5 (6.4)	6.8 (6.9)
3, 12	10.7 (11.6)	10.6 (11.9)	5.6 (4.9)
12, 11	10.7 (11.5)	10.6 (11.9)	10.2 (12.0)
4, 5[d]	1.5 (3.1)	0 (2.4)	6.8 (6.8)
4, 5[d]	7.6 (5.1)	7.5 (5.0)	12.9 (12.9)

[a] 500 MHz, $CDCl_3$; atom numbering as indicated in **17** (Scheme 2). – [b] MacroModel, see reference [32]. – [c] Assigned via H,H-COSY. – [d] Interchangeable.

Fortunately, the ^{1}H NMR spectroscopic data in the **b**-series are sufficiently characteristic to allow an unambiguous structural assignment (Table 3). In the **c**-series, the spectroscopic and physical data of lactone **21c** were found identical with those of the same intermediate previously synthesised by Hart and Kozikowski[8b] and by Chackalamannil;[9b] also **20c** was found identical with the compound described by the former group.[8b] Intermediate **21c** has previously been converted into himbacine (**1**) by a sequence involving: (i) removal of the *N*-Boc protecting group (trifluoroacetic acid); (ii) *N*-methylation by reductive amination (ca 75% overall yield).[8,9] In consequence the present work also constitutes a novel formal total synthesis of (+)-himbacine: although the sequence is reasonably short (12 steps in the longest linear sequence), the overall yield is low (8%) due to the lack in stereoselectivity of the intramolecular Diels–Alder process.

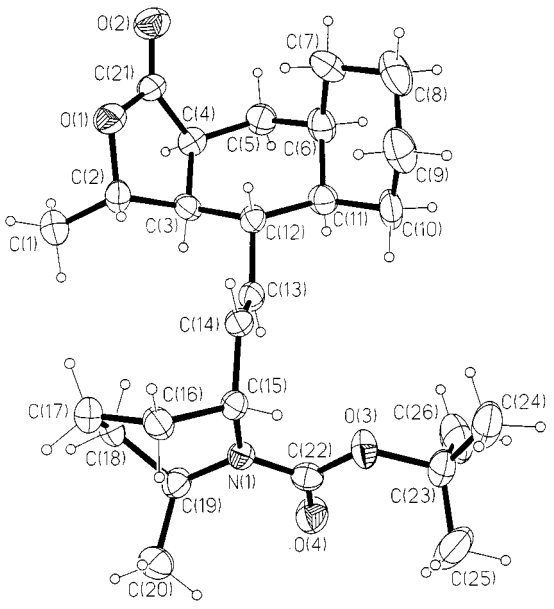


Figure 3. Perspective view of the crystal structure of **21a** with the adopted atom numbering

Conclusion

In the present work a concise convergent route has been developed for the preparation of **5**, an advanced Diels–Alder precursor for synthetic work in the area of himbacine. The stereochemical outcome of the cycloaddition reaction of **5** was studied in detail: The major isomeric adducts were converted into the corresponding lactones **21a**, **21b** and **21c**, which can be considered as direct precursors of himbacine and two stereoisomeric analogues. The biological evaluation of the latter will be reported in due course.

Experimental Section

All reactions were carried out under argon atmosphere with magnetic stirring. All solvents were purified or dried according to standard literature procedures. Solutions were dried with $MgSO_4$ (unless otherwise specified) and solvent evaporations were carried out in a Rotavapor at 16 Torr. – Column chromatography was performed on SiO_2. HPLC separations were performed on a Knauer

64 or a Kontron 420 delivery system with RI detection. − Optical rotations were measured with a Perkin−Elmer 421 polarimeter. − IR spectra were recorded on a Perkin−Elmer FTIR-1600 spectrometer, mass spectra on a HP-5988 spectrometer. − The ^{1}H NMR spectra were recorded at 500 MHz (Bruker AN-500), the ^{13}C NMR spectra at 50 MHz (Varian Gemini-200). The chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. − Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France).

(5*S*)-5-Methyl-3-tributylstannylfuran-2(5*H*)-one (10) and its Regioisomer (5*S*)-5-Methyl-4-tributylstannylfuran-2(5*H*)-one (10′): A solution of tributyltin hydride (1.024 g, 3.52 mmol) in dry THF (3.5 mL) was added over a period of 15 min to an orange solution of tetrakis(triphenylphosphane)palladium(0) (81.3 mg, 0.07 mmol) and ester **13**[19] (0.50 g, 3.52 mmol) in dry THF (3.5 mL). After stirring for 4 h at room temp., the reaction mixture was concentrated under argon. The residue was dissolved in cold pentane (−10 °C) and the organic phase filtered through Celite. The solvent was removed under reduced pressure and the residue separated by silica gel column chromatography with pentane/EtOAc (96:4) as eluent. The regioisomeric butenolides **10** (1.090 g, 80%) and **10′** (0.136 g, 10%) were obtained as colourless oils.

Compound 10:[17] R_f = 0.23 (pentane/EtOAc, 96:4). − $[\alpha]_D^{20}$ = +32.4 (c = 1.33, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 2957 (s), 2928 (s), 1738 (s), 1581 (m), 1464 (m), 1376 (m), 1305 (m), 1259 (m), 1146 (s), 1114 (m), 1089 (m), 965 (s), 874 (m), 774 (m), 695 (m), 663 (m) cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (m, 9 H), 1.08 (m, 6 H), 1.31 (m, 6 H), 1.40 (d, J = 6.8 Hz, 3 H), 1.45−1.58 (m, 6 H), 5.07 (dq, J = 1.2, 6.8 Hz, 1 H), 7.44 (d, J = 1.14, J(Sn) = 22.6 Hz, 1 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 9.6 (CH_2), 13.7 (CH_3), 19.2 (CH_3), 27.2 (CH_2), 28.7 (CH_2), 81.2 (CH), 134.8 (C), 166.6 (CH), 177.9 (C). − MS: m/z (%) = 387 (1) [M$^+$], 331 (100), 273 (21), 217 (59), 189 (36), 173 (16), 137 (22), 121 (29), 69 (12), 41 (48).

Compound 10′: R_f = 0.16 (pentane/EtOAc, 96:4). − IR (neat): $\tilde{\nu}$ = 2957 (s), 2928 (s), 1738 (s), 1581 (m), 1464 (m), 1376 (m), 1305 (m), 1259 (m), 1146 (s), 1114 (m), 1089 (m), 965 (s), 874 (m), 774 (m), 695 (m), 663 (m) cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (m, 9 H), 1.07 (m, 6 H), 1.32 (m, 6 H), 1.41 (d, J = 6.9 Hz, 3 H), 1.44−1.58 (m, 6 H), 5.18 (dq, J = 1.8, 6.9 Hz, 1 H), 6.12 (d, J = 1.87, J (Sn) =22.2 Hz, 1 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$) = 10.0 (CH_2), 13.6 (CH_3), 19.6 (CH_3), 27.2 (CH_2), 28.9 (CH_2), 86.0 (CH), 129.5 (CH), 173.0 (C), 179.1 (C). − MS: m/z (%) = 387 (1) [M$^+$], 331 (100), 273 (21), 217 (59), 189 (36), 173 (16), 137 (22), 121 (29), 69 (12), 41 (48).

(*E*,*E*)-1,8-Diiodo-1,7-octadiene (11), Method A: Diisobutylaluminum hydride (9.9 mL of a 1 M solution in hexane, 9.90 mmol) was added dropwise to a solution of 1,7-octadiyne (0.500 g, 4.71 mmol), in cyclohexane (10 mL), while the temperature was kept below 40 °C. The reaction mixture was stirred for a further 2 h at 50 °C. The solvent was removed under reduced pressure and the residue dissolved in THF (20 mL). To the cooled solution (−50 °C), a solution of iodine (2.538 g, 10.0 mmol) in THF (20 mL) was added dropwise. Subsequently, the reaction mixture was slowly warmed to room temp. and a dilute (20%) solution of sulfuric acid added dropwise. During this period the temperature was kept between 20 and 30 °C. When no further evolution of gas was observed during the addition, the mixture was poured into an ice-cold dilute (20%) solution of sulfuric acid (100 mL). After extraction of the aqueous phase with pentane (3 times 100 mL), the combined organic phases were washed consecutively with a saturated solution of sodium thiosulfate (150 mL) and sodium bicarbonate (150 mL). After concentration under reduced pressure, the residue was purified by distillation in vacuo to afford diiodide **11** (1.17 g, 69%) as a colourless oil. The product should be stored in the dark (−10 °C) on a trace of red copper powder. **Method B:** To a white suspension of bis(cyclopentadienyl)zirconium chloride hydride (Schwartz reagent; 5.00 g, 19.39 mmol; prepared by lithium aluminumhydride reduction of bis(cyclopentadienyl)zirconium dichloride according to [34]) in freshly distilled benzene (40 mL) was added under argon a solution of 1,7-octadiyne (0.858 g, 8.08 mmol) in benzene (10 mL). After stirring for 10 min at 40 °C, iodine (4.921 g, 19.39 mmol) was added and the brown reaction mixture was stirred for a further 15 min. The mixture was poured into hexane (200 mL) and after stirring for 10 min the precipitate was filtered on a column of Florisil. The deep purple filtrate was washed with a saturated solution of sodium thiosulfate and dried ($MgSO_4$). After filtration and concentration in vacuo, diiode **11** (2.5 g, 86%) was obtained sufficiently pure (^{1}H NMR) for immediate further use.

Compound 11: R_f = 0.56 (isooctane). − B.p. = 115 °C (0.1 Torr). − IR (neat): $\tilde{\nu}$ = 3045 (m), 2928 (s), 2854 (s), 1604 (m), 1457 (m), 1433 (m), 1213 (s), 945 (s), 658 (m) cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (m, 4 H), 2.05 (m, 4 H), 5.98 (d, J = 14.4 Hz, 2 H), 6.48 (dd, J = 7.2, 14.3 Hz, 2 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 27.6 (CH_2), 36.8 (CH_2), 74.8 (CH), 146.0 (CH). − MS: m/z (%) = 235 (7), 180(12), 167 (100), 154 (9), 127 (10), 107 (75), 93 (28), 79 (89), 67 (71), 53 (32).

***N*-Boc Protected Piperidine 12:** A solution of (trimethylsilyl)diazomethane (3.43 mL of a 2M solution in THF, 6.86 mmol) was added dropwise to a solution of lithium diisopropylamide (3.43 mL of a 2 M solution in THF, 6.86 mmol) in THF (10 mL) at −78 °C under argon. After stirring for 30 min at −78 °C a solution of aldehyde **15** (1.400 g, 6.16 mmol)[9] in THF was slowly added. After stirring for 1 h at −78 °C, the reaction mixture was heated at reflux for 3 h. After addition of water (20 mL), the mixture was extracted with diethyl ether (3 times 20 mL) and the combined organic phases were dried ($MgSO_4$). After filtration and concentration under reduced pressure the residue was separated by silica gel chromatography with isooctane/EtOAc (85:15) as eluent to afford pure alkyne **12** (1.034 g, 75%). − R_f = 0.23 (isooctane/EtOAc, 95:5). − $[\alpha]_D^{20}$ = +86.7 (c = 0.18, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3242 (s), 2936 (s), 1682 (s), 1455 (m), 1391 (s), 1310 (m), 1252 (m), 1173 (s), 1113 (s), 1080 (s), 881 (m), 770 (m), 710 (m) cm^{-1}. − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.7 Hz, 3 H), 1.47 (s, 9 H), 1.58−1.72 (m, 2 H), 1.79−1.92 (m, 3 H), 2.12 (m, 1 H), 2.22 (d, J = 2.3 Hz, 1 H), 3.96 (m, 1 H), 4.83 (m, 1 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 15.2 (CH_2), 21.2 (CH_3), 27.3 (CH_2), 28.5 (CH_3), 43.6 (CH), 48.1 (CH), 70.2 (C), 79.8 (C), 84.4 (CH), 155.1 (C). − MS: m/z (%) = 207 (4) [M$^+$], 167 (17), 152 (34), 149 (25), 143 (22), 122 (9), 108 (19), 91 (18), 69 (17), 57 (100). − $C_{13}H_{21}NO_2$ (223.31): calcd. C 69.92, H 9.48, N 6.27; found C 70.00, H 9.42, N 6.33.

The Sonogashira Coupling of Vinylic Diiodide 11 and Alkyne 12 to Enyne 16: Diiodide **11** (2.237 g, 6.18 mmol) and tetrakis(triphenylphosphane)palladium(0) (178 mg, 0.15 mmol) were dissolved in pyrrolidine (5 mL) at room temp. under argon. A solution of alkyne **12** (0.690 g, 3.09 mmol) in pyrrolidine (5 mL) was added and the mixture was stirred overnight. The reaction mixture was poured into water (10 mL), extracted with diethyl ether (3 times 15 mL) and dried ($MgSO_4$). Separation by silica gel column chromatography with isooctane/EtOAc (95:5) as eluent afforded enyne **16** (890 mg, 63%). − R_f = 0.32 (isooctane/EtOAc, 96:4). − $[\alpha]_D^{20}$ = +76.5 (c = 0.52, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 2932 (s), 2859 (s), 1682

(s), 1606 (m), 1455 (s), 1386 (s), 1307 (s), 1162 (s), 1070 (s), 1009 (m), 953 (s), 860(m), 772 (m), 659 (m) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.7 Hz, 3 H), 1.38 (m, 4 H), 1.46 (s, 9 H), 1.66 (m, 1 H), 1.78−1.87 (m, 3 H), 2.05 (m, 6 H), 3.88 (m, 1 H), 4.95 (br. s, 1 H), 5.45 (dd, *J* = 1.5, 15.8 Hz, 1 H), 5.97 (d, *J* = 14.4 Hz, 1 H), 6.04 (td, *J* = 7.1, 15.8 Hz, 1 H), 6.48 (td, *J* = 7.2, 14.3 Hz, 1 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 15.8 (CH_2), 21.2 (CH_3), 27.7 (CH_2), 27.9 (CH_2), 28.2 (CH_2), 28.5 (CH_3), 30.0 (CH_2), 32.6 (CH_2), 35.8 (CH_2), 44.6 (CH), 48.2 (CH), 74.6 (CH), 79.6 (C), 80.9 (C), 88.4 (C), 109.8 (CH), 143.7 (CH), 146.3 (CH), 155.1 (C).

The Stille Coupling of the Tributylstannyl Derivative 10 and Vinyl Iodide 16: A solution of butenolide **10** (0.875 g, 2.26 mmol) and iodide **16** (1.034 g, 2.26 mmol) in DMF (6 mL) was heated under argon at 65 °C. After addition of copper(I) chloride (0.556 g, 5.62 mmol) in one portion, the yellow reaction mixture was stirred at 65 °C for 2 h. The mixture was cooled to room temp. and poured into a saturated solution of ammonium chloride (20 mL). After extraction of the aqueous phase with diethyl ether (3 times 20 mL) and drying ($MgSO_4$), the solvents were removed under reduced pressure and the residue separated by silica gel chromatography with isooctane/EtOAc (9:1) as eluent. The desired enyne **5** (0.773 g, 80%) was obtained as a pale yellow oil. Compound **5:** R_f = 0.27 (isooctane/EtOAc, 8:2). − $[\alpha]_D^{20}$ = +99.8 (*c* = 0.89, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 2934 (s), 2859 (s), 1760 (s), 1690 (s), 1605 (w), 1454 (m), 1386 (m), 1308 (m), 1174 (m), 1084 (m), 1030 (m), 956 (m), 882 (m), 772 (m) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (m, 1 H), 1.26 (d, *J* = 6.7 Hz, 3 H), 1.37−1.48 (m, 5 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.45 (s, 9 H), 1.66 (m, 1 H), 1.83 (m, 2 H), 2.07 (m, 3 H), 2.15 (m, 2 H), 3.88 (m, 1 H), 4.94 (br. s, 1 H), 5.02 (br. q, *J* = 6.9 Hz, 1 H), 5.45 (dd, *J* = 1.4, 15.8 Hz, 1 H), 6.05 (td, *J* = 7.1, 15.6 Hz, 1 H), 6.08 (d, *J* = 15.8 Hz, 1 H), 6.77 (td, *J* = 7.0, 15.9 Hz, 1 H), 7.04 (br. s, 1 H). − ^{13}C NMR/DEPT (50 MHz, $CDCl_3$): δ = 15.8 (CH_2), 19.2 (CH_3), 21.2 (CH_3), 27.8 (CH_2), 28.15 (CH_2), 28.24 (CH_2), 28.28 (CH_2), 28.5 (CH_3), 32.8 (CH_2), 33.2 (CH_2), 44.7 (CH), 48.3 (CH), 76.9 (CH), 79.6 (C), 81.0 (C), 88.3 (C), 109.7 (CH), 118.6 (CH), 129.2 (C), 138.2 (CH), 143.8 (CH), 147.0 (CH), 155.1 (C), 171.9 (C). − MS: *m*/*z* (%) = 371 (10), 361 (18), 326 (20), 312 (9), 306 (7), 284 (6), 269 (10), 234 (51), 216 (30), 207 (32), 166 (29), 142 (41), 120 (27), 98 (75), 91 (70), 57 (100), 41 (40). − $C_{26}H_{37}NO_4$ (427.58): calcd. C 73.04, H 8.72, N 3.27; found C 72.99, H 8.89, N 3.08.

The Intramolecular Cycloaddition of 5, Followed by the Magnesium/Methanol Reduction of the Obtained Adducts: A solution of compound **5** (0.12 g, 0.28 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO; 20 mg) in toluene (150 mL) was heated under reflux for 72 h. After removal of the solvent under reduced pressure, the residue was separated by chromatography on silica gel with EtOAc/isooctane (1:8) as eluent. The cycloadducts **17** (96 mg, 80%) were obtained as a mixture of four stereoisomers (ratio 10:7:5:1 by ^1H NMR; R_f = 0.38 in EtOAc/isooctane, 1:3) next to starting material (13 mg, 11%). Magnesium (20 mg, 0.82 mmol) was added to a solution of **17** (80 mg, 0.19 mmol) in dry methanol (4 mL). The mixture was stirred at room temp. for 3 h, during which period two portions of magnesium (15 mg each) were further added. The reaction mixture was diluted with diethyl ether (5 mL) and filtered consecutively through a pad of Celite and of silica gel. After concentration of the filtrate under reduced pressure, the obtained residue was further separated by HPLC with acetone/isooctane (1:9) as eluent affording lactones **18a** (32 mg, 40%), **18b** (17 mg, 21%) and **18c** (25 mg, 31%) as major stereoisomers. Minor amounts of **18d** (2 mg, 2%), **18e** (2 mg, 2%) and **18f** (2 mg, 2%) were also obtained.

Compound 18a: R_f = 0.55 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +123 (*c* = 0.153, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2932 (s), 2860 (m), 1778 (s), 1694 (s), 1450 (w), 1389 (s), 1142 (m) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 1.10−1.90 (m, 15 H), 1.27 (d, *J* = 6.7 Hz, 3 H), 1.37 (d, *J* = 6.7 Hz, 3 H), 1.48 (s, 9 H), 2.04−2.12 (m, 2 H), 2.06 (d, *J* = 14.4 Hz, 1 H), 2.11 (dd, *J* = 7.5, 11.4 Hz, 1 H), 2.55 (t, *J* = 11.4 Hz, 1 H), 2.75 (dt, *J* = 1.8, 7.5 Hz, 1 H), 3.91 (qd, *J* = 6.7, 10.8 Hz, 1 H), 4.66 (q, *J* = 6.7 Hz, 1 H), 4.80 (br. s, peak width 10 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3, 19.5, 20.0, 21.3, 26.3, 27.0, 27.5, 27.8, 28.5, 29.4, 34.6, 35.5, 37.9, 43.9, 47.8, 47.9, 79.6, 83.0, 83.1, 155.1, 178.4. − MS: *m*/*z* (%) = 373 (3) [M^+ − 56], 329 (4), 314 (5), 284 (3), 220 (1), 181 (12), 142 (8), 98 (12), 57 (100).

Compound 18b: R_f = 0.49 (isooctane/EtOAc, 2:1). − M.p. 77 °C. − $[\alpha]_D^{20}$ = +50.0 (*c* = 0.388, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2932 (s), 2845 (m), 1778 (s), 1694 (s), 1455 (m), 1390 (s), 1361 (m), 1308 (w), 1180 (s), 1126 (m), 1061 (m), 874 (w) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$)= 1.1−2.0 (m, 15 H), 1.24 (d, *J* = 6.7 Hz, 3 H), 1.45 (s, 9 H), 1.59 (d, *J* = 6.7 Hz, 3 H), 2.08 (d, *J* = 13.9 Hz, 1 H), 2.11 (m, 1 H), 2.20 (br. d, *J* = 13.1 Hz, 1 H), 2.40 (ddd, *J* = 4.7, 7.2, 11.2 Hz, 1 H), 2.54 (t, *J* = 11.2 Hz, 1 H), 2.67 (t, *J* = 7.2 Hz, 1 H), 3.89 (qd, *J* = 6.7, 11.3 Hz, 1 H), 4.55 (qd, *J* = 4.7, 6.7 Hz, 1 H), 4.78 (br. s, half width = 8 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1, 16.4, 19.9, 21.2, 23.5, 26.6, 26.8, 27.3, 27.6, 28.1, 28.4, 29.1, 34.9, 38.8, 39.8, 43.6, 45.6, 47.9, 78.4, 79.5, 83.7, 84.2, 155.0, 178.6. − MS = *m*/*z* (%) = 373 (1) [M^+ − 56], 329 (1), 314 (2), 284 (1), 257 (2), 193 (4), 166 (4), 142 (10), 111 (18), 57 (100). − $C_{26}H_{39}NO_4$ (429.58): calcd. C 72.69, H 9.15, N 3.26; found C 72.64, H 8.96, N 2.99.

Compound 18c: R_f = 0.51 (isooctane/EtOAc, 2:1). − M.p. 145 °C. − $[\alpha]_D^{20}$ = +111 (*c* = 0.695, $CHCl_3$). − IR (CH_2Cl_2) = 2932 (s), 2857 (m), 1778 (s), 1690 (s), 1451 (w), 1389 (s), 1364 (s), 1309 (m), 1271 (m), 1176 (s), 1125 (w), 1065 (m), 955 (m) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 0.8−2.0 (m, 17 H), 1.26 (d, *J* = 6.7 Hz, 3 H), 1.47 (s, 9 H), 1.63 (d, *J* = 6.0 Hz, 3 H), 2.22 (br. d, *J* = 13.3 Hz, 1 H), 2.42 (m, 2 H), 2.58 (td, *J* = 6.4, 12.8 Hz, 1 H), 3.92 (m, 1 H), 4.65 (qd, *J* = 6.0, 9.8 Hz, 1 H), 4.82 (br. s, half width = 10 Hz, 1 H). − ^1H NMR/H,H-COSY (500 MHz, C_6D_6): δ = 0.32 (m, 1 H), 0.5−1.75 (m, 15 H), 1.25 (d, *J* = 6.7 Hz, 3 H), 1.47 (s, 9 H), 1.57 (d, *J* = 6.0 Hz, 3 H), 1.80 (*A*Bdd, *J* = 10.2, 6.7, 5.4 Hz, 1 H), 1.86 (A*B*dd, *J* = 11.1, 5.4, 2.0 Hz, 1 H), 2.03 (m, 1 H), 2.09 (td, *J* = 6.7, 13.0 Hz, 1 H), 2.22 (br. d, *J* = 13.0 Hz, 1 H), 3.99 (qd, *J* = 6.7, 9.8 Hz, 1 H), 4.24 (qd, *J* = 6.0, 10.2 Hz, 1 H), 4.98 (br. s, half width = 8 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.9, 21.1, 21.4, 26.0, 26.3, 27.1, 27.3, 28.5, 31.3, 31.8, 33.4, 34.0, 39.9, 41.4, 42.5, 43.3, 45.7, 47.9, 79.7, 79.7, 81.6, 85.4, 154.9, 177.7. − MS *m*/*z* (%) = 373 (4) [M^+ − 56], 328 (9), 314 (12), 284 (2), 238 (1), 230 (1), 149 (15), 117 (8), 91 (18), 57 (100). − $C_{26}H_{39}NO_4$ (429.58): calcd. C 72.69, H 9.15, N 3.26, found C 72.64, H 9.23, N 3.30.

Compound 18d: R_f = 0.52 (isooctane/EtOAc, 2:1). − [a]$_D^{20}$ = −19.0 (*c* = 0.179, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2932 (s), 2856 (m), 1776 (s), 1690 (s), 1391 (m), 1364 (m), 1334 (m), 1195 (m), 1080 (w), 956 (m) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, C_6D_6): δ = 0.3 (m, 1 H), 0.4−2.0 (m, 17 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.49 (s, 9 H), 1.60 (d, *J* = 5.9 Hz, 3 H), 1.66 (br. d, *J* = 12.8 Hz, 1 H), 2.08 (td, *J* = 6.5, 13.1 Hz, 1 H), 2.17 (br. d, *J* = 12.2 Hz, 1 H), 4.23 (qd, *J* = 5.9, 9.9 Hz, 1 H), 4.43 (br. s, 1 H), 5.14 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1, 18.9, 21.7, 26.0, 26.2, 28.4, 30.0, 30.7, 31.3, 31.8, 33.4, 34.0, 35.3, 39.8, 41.4, 42.1, 45.5, 46.7, 79.8, 81.2, 86.4, 154.8, 177.7. − MS: *m*/*z* (%) = 373 (4) [M^+ − 56], 356

(1), 345 (1), 328 (4), 314 (12), 284 (2), 193 (4), 148 (15), 91 (15), 57 (100).

Compound 18e: R_f = 0.55 (isooctane/EtOAc; 2:1). − $[\alpha]_D^{20}$ = +53.6 (c = 0.425, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2932 (s), 2860 (m), 1776 (s), 1694 (s), 1450 (w), 1391 (m), 1354 (m), 1310 (w), 1257 (w), 1182 (m), 999 (w), 955 (w) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 1.1−1.95 (m, 16 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.46 (s, 9 H), 1.60 (d, J = 6.1 Hz, 3 H), 1.99 (m, 1 H), 2.12 (m, 1 H), 2.22 (br. d, J = 13.5 Hz, 1 H), 2.31 (dt, J = 3.4, 12.9 Hz, 1 H), 2.63 (dt, J = 1.4, 11.0 Hz, 1 H), 3.90 (qd, J = 6.7, 11.2 Hz, 1 H), 4.33 (qd, J = 6.1, 9.8 Hz, 1 H), 4.81 (br. s, half width = 9.5 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.9, 19.4, 20.7, 21.1, 26.7, 26.9, 27.1, 27.3, 28.3, 28.5, 30.3, 30.6, 36.1, 41.3, 42.1, 43.4, 47.8, 54.7, 79.7, 81.0, 81.7, 84.7, 154.9, 176.6. − MS: m/z (%) = 373 (7) [M^+ − 56], 356 (2), 328 (4), 314 (8), 277 (4), 261 (6), 248 (2), 234 (3), 220 (10), 207 (3), 193 (5), 181 (10), 142 (10), 91 (12), 57 (100).

Compound 18f: R_f = 0.55 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +59.6 (c = 0.685, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2931 (s), 2864 (m), 1778 (s), 1693 (s), 1451 (w), 1390 (s), 1365 (s), 1312 (w), 1254 (w), 1166 (m), 1123 (w), 1042 (w), 959 (w) cm^{-1}. − ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 1.2−2.2 (m, 19 H), 1.25 (d, J = 6.6 Hz, 3 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.47 (s, 9 H), 2.37 (ddd, J = 3.5, 10.6, 12.3 Hz, 1 H), 2.59 (t, J = 11.4 Hz, 1 H), 3.89 (qd, J = 6.6, 11.2 Hz, 1 H), 4.74 (dq, J = 6.7, 6.7 Hz, 1 H), 4.78 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 15.2, 20.8, 21.2, 26.7, 26.9, 27.4, 27.7, 28.3, 28.5, 28.7, 31.0, 35.8, 36.3, 42.0, 43.7, 47.8, 50.5, 79.6, 80.9, 83.6, 155.1, 177.3. − MS m/z (%) = 373 (4) [M^+ − 56], 358 (1), 330 (1), 314 (5), 300 (1), 279 (2), 261 (2), 220 (8), 181 (8), 142 (8), 91 (10), 57 (100).

The Conversion of Lactones 18 into Acetals 19: Diisobutylaluminum hydride (300 μL 1M in hexane, 0.3 mmol) was slowly added at −78 °C to a stirred solution of lactone **18c** (0.061 g, 0.142 mmol) in toluene (2 mL). After stirring for 1 h at −78 °C the mixture was quenched with methanol (50 μL) and filtered through a pad of Celite and silica gel. After washing with EtOAc, the filtrate was concentrated under reduced pressure. To a solution of the residue in methanol (4 mL) were added at 0 °C boron trifluoride diethyl etherate (2 μL) and dichloromethane (0.8 mL). The mixture was warmed to room temp. over a period of 3 h and quenched with sodium bicarbonate (0.02 g). The mixture was filtered through a pad of silica gel. Concentration of the filtrate under reduced pressure afforded a residue which was further separated on HPLC with acetone/isooctane (1:45) as eluent to yield acetal **19c** (0.061 g, 96%). In the same manner as described above lactones **18a** and **18b** were transformed into **19a** (2 stereoisomers at the acetal carbon) and **19b**, respectively.

Compound 19a: *Isomer 1*, obtained in 82% yield. R_f = 0.63 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +112 (c = 0.496, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2928 (s), 2856 (m), 1694 (s), 1454 (m), 1389 (s), 1361 (m), 1308 (m), 1256 (m), 1177 (m), 1099 (m), 1061 (m), 1000 (w), 975 (w), 932 (w) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.2−2.2 (m, 19 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.28 (d, J = 6.2 Hz, 3 H), 1.46 (s, 9 H), 2.34 (m, 1 H), 2.44 (t, J = 7.2 Hz, 1 H), 3.34 (s, 3 H), 3.88 (qd, J = 6.7, 12.3 Hz, 1 H), 4.20 (qd, J = 6.2, 6.2 Hz, 1 H), 4.66 (d, J = 2.8 Hz, 1 H), 4.78 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.6, 21.3, 22.5, 23.4, 24.2, 27.5, 27.8, 28.0, 28.5, 29.0, 30.5, 30.6, 32.7, 39.7, 43.2, 44.1, 48.0, 49.9, 55.1, 79.5, 80.4, 81.7, 85.4, 110.1, 155.2. − MS: m/z (%) = 414 (0.2) [M^+ − 31], 388 (0.5), 357 (8), 312 (3), 298 (10), 284 (4), 256 (2), 216 (3), 188 (3), 153 (9), 142 (25), 98 (18), 57 (100).

Compound 19a: *Isomer 2*, obtained in 14% yield. R_f = 0.65 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +47.4 (c = 0.870, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2926 (s), 2856 (m), 1694 (s), 1456 (m), 1386 (s), 1308 (w), 1178 (m), 1068 (s), 1032 (s) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.2−1.9 (m, 18 H), 1.26 (d, J = 6.7 Hz, 3 H), 1.31 (d, J = 6.2 Hz, 3 H), 1.47 (s, 9 H), 2.12 (m, 1 H), 2.26 (dt, J = 1.8, 8.9 Hz, 1 H), 2.41 (m, 1 H), 3.33 (s, 3 H), 3.90 (m, 1 H), 3.99 (qd, J = 6.2, 6.2 Hz, 1 H), 4.81 (m, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4, 21.2, 21.5, 22.7, 23.4, 24.4, 27.6, 27.8, 28.5, 29.0, 30.8, 32.6, 35.1, 40.0, 43.2, 44.0, 47.9, 48.0, 54.8, 78.6, 79.4, 81.5, 85.4, 105.5, 155.1. − MS: m/z (%) = 445 [M^+], 414 (0.1), 388 (1), 358 (4), 357 (16), 340 (2), 314 (2), 298 (2), 284 (2), 270 (2), 256 (2), 218 (2), 173 (2), 142 (24), 57 (100).

Compound 19b: Obtained in 96% yield. R_f = 0.68 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +43.0 (c = 0.493, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2927 (s), 2861 (m), 1694 (s), 1450 (m), 1388 (s), 1365 (s), 1309 (w), 1177 (m), 1096 (m), 1061 (m), 1003 (m) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.2−2.0 (m, 16 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.43 (d, J = 6.6 Hz, 3 H), 1.46 (s, 9 H), 2.05 (ddd, J = 10.9, 7.1, 4.3 Hz, 1 H), 2.12 (m, 1 H), 2.23 (br. d, J = 12.5 Hz, 1 H), 2.25 (m, 1 H), 2.50 (t, J = 11.9 Hz, 1 H), 3.37 (s, 3 H), 3.90 (m, 1 H), 4.27 (dq, J = 4.3, 6.6 Hz, 1 H), 4.68 (d, J = 4.8 Hz, 1 H), 4.79 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3, 16.7, 20.4, 21.3, 23.5, 26.9, 27.5, 27.7, 28.2, 28.5, 29.2, 30.1, 35.0, 38.9, 43.9, 45.0, 47.6, 47.9, 55.7, 79.4, 82.7, 85.8, 109.3, 155.1. − MS: m/z (%) = 445 [M^+], 414 (1), 388 (4), 357 (10), 330(4), 312 (8), 298 (11), 270 (4), 257 (8), 220 (3), 216 (4), 188 (10), 142 (25), 91 (15), 57 (100).

Compound 19c: R_f = 0.64 (isooctane/EtOAc, 2:1). − $[\alpha]_D^{20}$ = +141 (c = 0.380, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2929 (s), 2855 (m), 1694 (s), 1453 (m), 1387 (s), 1308 (m), 1176 (m), 1122 (m), 1102 (m), 1063 (m), 980 (m), 942 (m), 773 (w) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 0.8−2.0 (m, 16 H), 1.25 (d, J = 6.7 Hz, 3 H), 1.43 (d, J = 6.0 Hz, 3 H), 1.45 (s, 9 H), 2.12 (m, 3 H), 2.36 (m, 2 H), 3.31 (s, 3 H), 3.90 (m, 1 H), 4.15 (m, 1 H), 4.48 (s, 1 H), 4.80 (br. s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1, 21.2, 24.5, 26.3, 26.5, 27.4, 27.5, 28.5, 31.5, 32.9, 33.8, 34.6, 40.0, 42.3, 43.6, 45.7, 47.9, 54.0, 76.7, 79.5, 83.1, 83.9, 108.4, 155.0. − MS: m/z (%) = 445 [M^+], 414 (1), 388 (4), 357 (10), 330 (4), 312 (7), 298 (11), 270 (4), 257 (8), 220(3), 216 (4), 166 (10), 142 (20), 91 (15), 57 (100).

Reduction of Alkynes 19: A solution of acetal **19c** (0.030 g, 0.067 mmol) in THF (0.75 mL) was added dropwise to a solution of lithium (5 mg, 0.7 mmol), ammonium sulfate (0.120 g, 0.9 mmol) and *tert*-butyl alcohol (0.013 mL, 0.14 mmol) in liquid ammonia (4 mL) at −78 °C. The mixture was stirred at reflux for 1 h. The reaction mixture was quenched with water (20 μL), diluted with diethyl ether (4 mL) and filtered through a short silica gel column. After concentration of the filtrate under reduced pressure the residue was separated on HPLC with acetone/isooctane (1:40) to afford the (*E*)-alkene **20c** (0.029 g, 96%). In the same manner as described above acetals **19a** (major isomer) and **19b** were reduced to **20a** (98% yield) and **20b** (96% yield), respectively.

Compound 20a: R_f = 0.60 (isooctane/EtOAc, 2:1). − M.p. 89−90 °C. − $[\alpha]_D^{20}$ = +72.4 (c = 0.293, $CHCl_3$). − IR (CH_2Cl_2): $\tilde{\nu}$ = 2928 (s), 2863 (m), 1693 (s), 1454 (m), 1392 (s), 1370 (m), 1310 (w), 1255 (w), 1180 (m), 1086 (m), 1046 (m), 1004 (w), 978 (w), 860 (w), 772 (w) cm^{-1}. − ^1H NMR (500 MHz, $CDCl_3$): δ = 1.2−1.8 (m, 17 H), 1.20 (d, J = 6.5 Hz, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.43 (s, 9 H), 1.87 (m, 1 H), 1.95 (m, 1 H), 2.10 (q, J = 9.0 Hz, 1 H), 2.31 (m, 1 H), 3.35 (s, 3 H), 4.01 (br. s, 1 H), 4.11 (dq, J = 4.4, 6.5 Hz, 1 H), 4.41 (br. s, 1 H), 4.72 (d, J = 3.6 Hz, 1 H), 5.19 (ddd, J = 1.4, 9.0, 15.4 Hz, 1 H), 5.45 (dd, J = 4.4, 15.4 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 20.9, 22.3, 22.8, 24.7, 25.5, 26.2, 28.0,

28.5, 28.9, 30.5, 33.1, 39.0, 40.5, 43.0, 47.0, 48.8, 52.2, 55.1, 78.9, 80.1, 110.5, 132.6, 133.2, 155.2. – MS: *m/z* (%) = 359 (14) [M^+ – 88], 331 (2), 300 (2), 286 (1), 218 (2), 168 (6), 142 (38), 98 (40), 57 (100). – $C_{27}H_{45}NO_4$ (447.65): calcd. C 72.44, H 10.13, N 3.13; found C 72.64, H 10.41, N 3.06.

Compound 20b: R_f = 0.63 (isooctane/EtOAc, 2:1). – $[\alpha]_D^{20}$ = +16.3 (*c* = 0.590, $CHCl_3$). – IR (CH_2CL_2): $\tilde{\nu}$ = 2927 (s), 2862 (s), 1693 (s), 1451 (w), 1392 (s), 1364 (s), 1314 (m), 1254 (m), 1179 (s), 1097 (s), 1062 (m), 1032 (w), 968 (m), 773 (w) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.2–2.0 (m, 19 H), 1.23 (d, *J* = 6.6 Hz, 3 H), 1.26 (d, *J* = 6.6 Hz, 3 H), 1.44 (s, 9 H), 2.25 (m, 1 H), 2.36 (q, *J* = 9.6 Hz, 1 H), 3.36 (s, 3 H), 4.00 (m, 1 H), 4.24 (dq, *J* = 6.6, 6.6 Hz, 1 H), 4.41 (br. s, 1 H), 4.71 (d, *J* = 4.1 Hz, 1 H), 5.13 (dd, *J* = 9.6, 15.6 Hz, 1 H), 5.43 (dd, *J* = 5.8, 15.6 Hz, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 18.1, 20.6, 20.9, 25.5, 26.3, 26.7, 28.1, 28.5, 29.0, 30.5, 33.8, 34.7, 38.1, 45.0, 46.1, 46.9, 52.5, 55.5, 77.5, 78.8, 109.2, 132.9, 134.7, 155.1. – MS: *m/z* (%) = 447 (0.4) [M^+], 416 (0.4), 390 (0.3), 362 (0.8), 359 (8), 330 (2), 300 (2), 286 (3), 218 (3), 168 (7), 142 (40), 88 (22), 57 (100).

Compound 20c:[8b] R_f= 0.45 (isooctane/EtOAc, 3:1). – $[\alpha]_D^{20}$ = +93.5 (*c* = 0.231, $CHCl_3$). – IR (CH_2Cl_2)= $\tilde{\nu}$ = 2930 (s), 2854 (m), 1693 (s), 1452 (m), 1390(s), 1361 (s), 1178 (m), 1100 (m), 1053 (m), 980 (m), 941 (m), 773 (w) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.69 (m, 1 H), 0.9–1.7 (m, 14 H), 1.23 (d, *J* = 6.7 Hz, 3 H), 1.29 (d, *J* = 6.0 Hz, 3 H), 1.44 (s, 9 H), 1.75 (d, *J* = 13.5 Hz, 1 H), 1.94 (m, 2 H), 2.05 (m, 1 H), 2.18 (m, 2 H), 3.31 (s, 3 H), 3.98 (m, 1 H), 4.18 (m, 1 H), 4.41 (m, 1 H), 4.48 (s, 1 H), 5.21 (ddd, *J* = 1.0, 9.9, 15.2 Hz, 1 H), 5.47 (dd, *J* = 6.3, 15.2 Hz, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.4, 20.9, 24.8, 25.8, 26.4, 26.5, 26.6, 28.5, 31.4, 33.1, 34.1, 40.3, 41.3, 46.4, 46.5, 47.0, 48.7, 52.4, 53.9, 75.6, 78.9, 108.4, 133.0, 155.1. – MS: *m/z* (%) = 448 [M^+], 374 (1), 358 (2), 332 (2), 315 (6), 300 (2), 272 (3), 258 (1), 232 (1), 218 (2), 195 (8), 142 (25), 111 (45), 88 (50), 57 (100).

The Oxidation of Acetals 20 into Lactones 21: A solution of acetal **20c** (0.023 g, 0.051 mmol) in acetone (2 mL) was added to a solution of Jones reagent [50 μL of a solution obtained by slowly adding 98% sulfuric acid (2.3 mL, 0.429 mmol) to a solution of chromium(III) oxide (5.15 g, 0.515 mmol) in water (15 mL)] in acetone (2 mL). The mixture was stirred at room temp. for 40 min. The reaction was quenched with 2-propanol (one drop), diluted with diethyl ether (5 mL), and filtered through a short silica gel column. After concentration of the filtrate under reduced pressure the residue was separated on HPLC with EtOAc/isooctane (1:6) as eluent to afford **21c** (22 mg, 99%) as a white solid. In the same manner as described above acetals **20a** and **20b** were oxidized to lactones **21a** (98% yield) and **21b** (97% yield), respectively.

Compound 21a: R_f = 0.46 (isooctane/EtOAc, 2:1). – M.p. 157–158 °C. $[\alpha]_D^{20}$ = +65.7 (*c* = 0.42, $CHCl_3$). – IR (CH_2Cl_2): $\tilde{\nu}$ = 2930 (s), 2864 (m), 1774 (s), 1688 (s), 1390 (s), 1364 (s), 1179 (m), 1147 (m), 1113 (w), 1094 (w), 970 (w), 773 (w) cm^{-1}. – ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 1.1–1.9 (m, 17 H), 1.24 (d, *J* = 6.7 Hz, 3 H), 1.26 (d, *J* = 6.6 Hz, 3 H), 1.44 (s, 9 H), 1.98 (m, 1 H), 2.08 (d, *J* = 14.3 Hz, 1 H), 2.17 (q, *J* = 10.7 Hz, 1 H), 2.75 (dt, *J* = 1.5, 7.6 Hz, 1 H), 4.06 (m, 1 H), 4.41 (m, 1 H), 4.47 (q, *J* = 6.6 Hz, 1 H), 5.06 (ddd, *J* = 1.4, 9.4, 15.4 Hz, 1 H), 5.56 (dd, *J* = 4.8, 15.4 Hz, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6, 19.3, 19.7, 20.8, 25.9, 26.2, 26.4, 27.3, 28.1, 28.5, 28.9, 34.8, 35.3, 37.4, 39.2, 45.9, 47.0, 52.2, 78.4, 79.1, 130.8, 135.6, 155.1, 179.1. – MS: *m/z* (%) = 431 [M^+], 375 (5), 358 (1), 331 (2), 316 (5), 286 (1), 232 (2), 218 (1), 185 (4), 151 (9), 124 (30), 98 (50), 57 (100). – $C_{26}H_{41}NO_4$ (431.62): calcd. C 72.35, H 9.57, N 3.24; found C 72.24, H 9.53, N 3.20.

Compound 21b: R_f = 0.44 (isooctane/EtOAc, 2:1). – $[\alpha]_D^{20}$ = +20.6 (*c* = 0.494, $CHCl_3$). – IR (CH_2Cl_2): $\tilde{\nu}$ = 2928 (s), 2862 (m), 1771 (s), 1692 (s), 1392 (s), 1363 (s), 1317 (w), 1258 (w), 1182 (m), 1089 (m), 859 (w), 773 (w), 731 (w) cm^{-1}. – ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 1.1–1.9 (m, 16 H), 1.23 (d, *J* = 6.6 Hz, 3 H), 1.42 (d, *J* = 6.8, 3 H), 1.44 (s, 9 H), 1.98 (m, 1 H), 2.09 (d, *J* = 14.1 Hz, 1 H), 2.23 (ddd, *J* = 4.8, 7.5, 10.6 Hz, 1 H), 2.46 (q, *J* = 10.6 Hz, 1 H), 2.68 (t, *J* = 7.5 Hz, 1 H), 4.01 (m, 1 H), 4.42 (br. s, 1 H), 4.51 (dq, *J* = 4.8, 6.6 Hz, 1 H), 5.13 (dd, *J* = 8.7, 15.6, 1 H), 5.47 (dd, *J* = 5.7, 15.6 Hz, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5, 17.7, 20.0, 20.9, 25.5, 26.3, 26.8, 27.2, 28.1, 28.3, 28.5, 33.0, 35.1, 38.2, 40.0, 44.4, 46.9, 52.5, 79.0, 79.2, 133.2, 134.2, 155.0, 179.2. – MS: *m/z* (%) = 375 (6) [M^+ – 56], 358 (2), 331 (5), 316 (10), 288 (4), 272 (1), 258 (2), 232 (4), 218 (3), 168 (12), 124 (30), 98 (25), 57 (100).

Compound 21c:[8b,9b] R_f = 0.45 (isooctane/EtOAc, 2:1). – $[\alpha]_D^{20}$ = +66.0 (*c* = 0.585, $CHCl_3$). – IR (CH_2Cl_2): $\tilde{\nu}$ = 2928 (s), 2855 (m), 1778 (s), 1682 (s), 1455 (m), 1392 (s), 1310 (w), 1178 (m), 1113 (w), 1064 (m), 1040 (m), 956 (m), 876 (w), 773 (w) cm^{-1}. – ^1H NMR/H,H-COSY (500 MHz, $CDCl_3$): δ = 0.69 (m, 1 H), 1.0–2.0 (m, 17 H), 1.24 (d, *J* = 6.7 Hz, 3 H), 1.42 (d, *J* = 6.0, 3 H), 1.44 (s, 9 H), 2.09 (dt, *J* = 5.6, 10.2 Hz, 1 H), 2.24 (ddd, *J* = 5.6, 6.8, 10.3 Hz, 1 H), 2.61 (td, *J* = 6.8, 12.9 Hz, 1 H), 4.00 (m, 1 H), 4.43 (br. s, 1 H), 4.64 (qd, *J* = 6.0, 10.3 Hz, 1 H), 5.23 (dd, *J* = 10.2, 15.2 Hz, 1 H), 5.53 (dd, *J* = 6.0, 15.2 Hz, 1 H). – ^{13}C NMR (50 MHz,$CDCl_3$): δ = 13.4, 20.9, 22.2, 25.6, 26.1, 26.3, 26.4, 28.5, 31.2, 32.0, 33.6, 40.0, 41.6, 42.3, 45.7, 47.0, 48.8, 52.2, 79.1, 131.3, 134.2, 155.0, 178.4. – MS: *m/z* (%) = 375 (12) [M^+ – 56], 358 (1), 331 (1), 316 (15), 286 (1), 232 (4), 195 (8), 151 (14), 124 (40), 98 (55), 57 (100).

X-ray Crystal Structure Analysis of 21a:[35] *Crystal Data:* $C_{26}H_{41}NO_4$; *M* = 431.62 g/mol; orthorhombic, space group $P2_12_12_1$, *a* = 11.298(2), *b* = 13.205(2), *c* = 17.403(4) Å, *V* = 2596.4(8) $Å^3$, *Z* = 4, $d_{calcd.}$ = 1.104 Mg/m^3. – *Data Collection:* Bruker P4 diffractometer, Mo-K_α radiation (λ = 0.71073 Å), graphite monochromator; crystal size 0.44×0.38×0.16 mm^3, μ = 0.073 mm^{-1}; ω scan mode, θ range: 1.9–25°, index ranges: $-1 \le h \le 13$, $-15 \le k \le 1$, $-20 \le l \le 1$, reflections collected: 3332, independent: 3140, observed reflections [$I > 2\sigma(I)$]: 1697; empirical absorption correction by ψ-scans. – *Structure Solution and Refinement:* solution by direct methods, refinement by full-matrix least-squares on F^2, non-H atoms with anisotropic displacement parameters, H atoms geometrically positioned and treated as riding atoms; data/parameters ratio: 3140/282; *R* = 0.0875 (observed data), $R_w(F^2)$ = 0.2932 (all data). Programs used: XSCANS,[36] SIR97,[37] SHELXTL/IRIS,[38] SHELXL-97,[39] MOLDRAW.[40]

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