Connective Synthesis of Spirovetivanes: Total Synthesis of (±)-Agarospirol, (±)-Hinesol and (±)-α-Vetispirene

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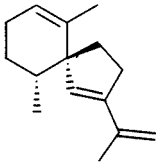
Dedicated with respect and admiration to Professor W. B. Motherwell

Keywords: Spiro compounds / Total synthesis / Spiroannulation / Orthoesters / Diastereocontrol

A concise, connective synthesis of naturally occurring spirovetivanes **1** and **3**, in racemic form, is presented. This novel approach involves the efficient assembly of the advanced intermediate **12** through a unique spiroannulation protocol.

Introduction

Molecules possessing a spirocyclic framework are ubiquitous in nature, many among them displaying interesting biological and odoriferous properties. For example, α-vetispirene (**1**), chamigrene (**2**), agarospirol (**3a**) and hinesol (**3b**) contain a spiro[4.5]decane or a spiro[5.5]undecane core embedded in their structures. It is therefore hardly surprising that a range of elegant strategies have been developed for the rapid assembly of such subunits.[1]



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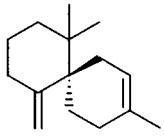

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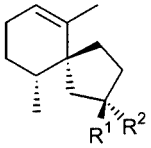

3a, $R^1 = C(CH_3)_2OH$, $R^2 = H$
3b, $R^1 = H$, $R^2 = C(CH_3)_2OH$

Recently we have reported an efficient and connective spiroannulation methodology that allows the expeditious construction of a variety of spirocyclic derivatives of different ring sizes.[2] This two-step approach involves the initial condensation between a silyl enol ether **4** and a functionalised orthoester **5**, followed by base-catalysed intramolecular cyclisation of the resulting β-keto ketals **6**, to afford, in good to excellent yields, monoprotected spiro diketones **7** (Scheme 1).

Furthermore, when 3-substituted silyl enol ethers such as **8** are employed, complete diastereocontrol is exercised both in the condensation and in the spiroannulation steps (Scheme 2).

The generation of diastereomerically pure, monoprotected spiro diketones such as **11a** provides an efficient access to the spiro[4.5] core present in several naturally occurring sesquiterpenes (Scheme 2).

In this communication, we wish to report our results in the successful attainment of this strategy, culminating in the total synthesis of (±)-agarospirol (**3a**), (±)-hinesol (**3b**)[3] and (±)-α-vetispirene (**1**).[4] Our proposed antithetic analysis is presented in Scheme 3. Ketone **12** was envisaged as being a key precursor that could, after appropriate functionalisation of the five-membered ring, lead to the desired products **1** and **3**. The spiro derivative **12** could conceivably derive from the masked diketone **11a**, itself readily accessible by our condensation/spiroannulation methodology. In this approach, the two crucial stereogenic centres, present in the cores of **1** and **3**, have been readily implemented at an early stage of the synthesis.

Our route towards the spirovetivanes **1** and **3** began with the zinc chloride catalysed condensation between the silyl enol ether **8a** (readily available by the addition of dimethyl cuprate to cyclohex-2-enone in the presence of Me_3SiCl)[5] and orthoester **9**, affording the desired β-keto ketal **10a** as

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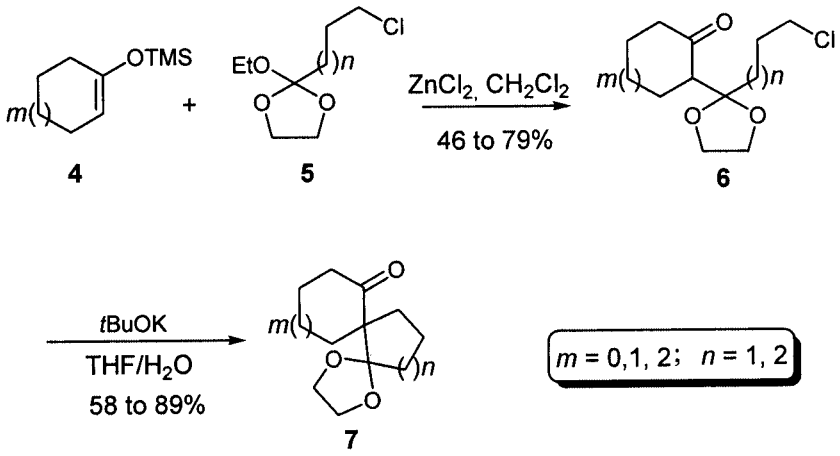
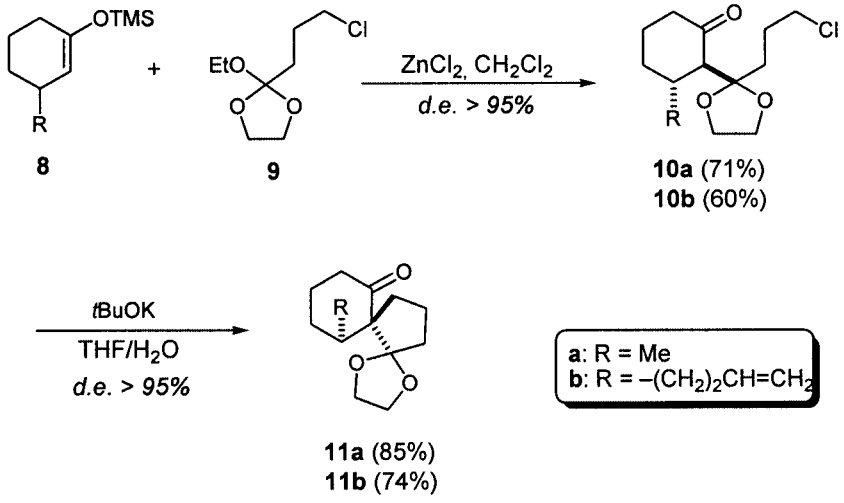
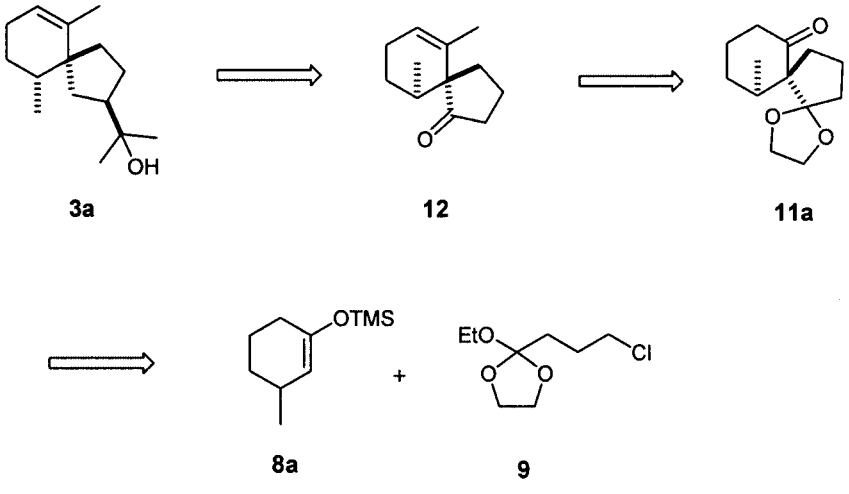


Scheme 1



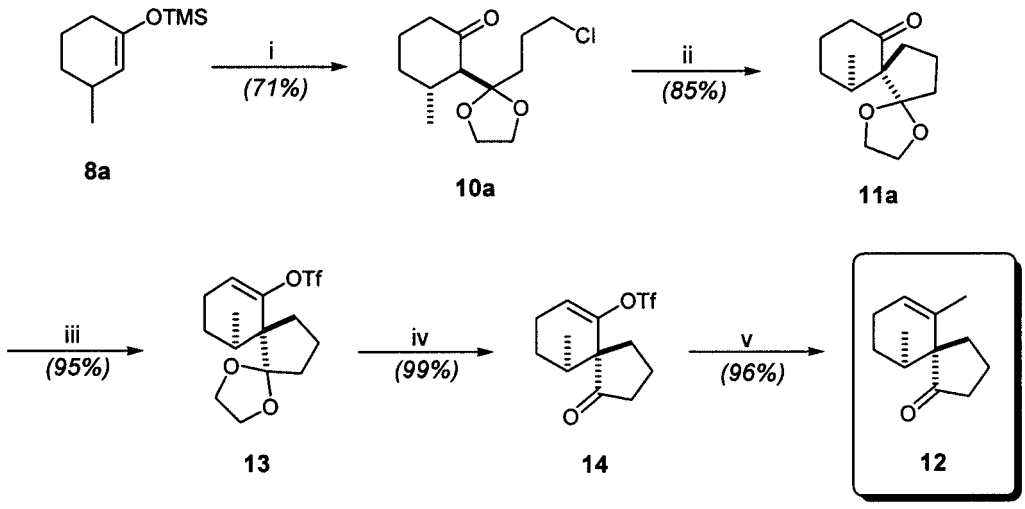
Scheme 2



Scheme 3

a single diastereoisomer in 71% yield (Scheme 4). Spirocyclisation of **10a** proceeded smoothly in the presence of potassium *tert*-butoxide in wet THF, to give the mono-protected diketone **11a** in 85% yield.[6]

It was anticipated that the introduction of the trisubstituted endocyclic double bond could be accomplished by acid-catalysed dehydration of the tertiary alcohol derived from ketone **11a**.[7] Unfortunately, despite considerable ef-



Scheme 4. Reagents and conditions: (i) $ZnCl_2$, **9**, CH_2Cl_2, room temperature; (ii) *t*BuOK, THF/H_2O, room temperature; (iii) potassium hexamethyl disilazane (KHMDS), $PhNTf_2$, THF, −78 °C to room temperature; (iv) ceric ammonium nitrate (CAN), CH_3CN/H_2O, 60 °C; (v) 20 mol % $Fe(acac)_3$, THF/*N*-methyl-2-pyrrolidinone (NMP), −15 °C to 0 °C.

forts only mixtures of exo- and endocyclic alkenes were obtained. Attention was therefore turned to the use of a coupling protocol between vinyl triflate **13** and a suitable organometallic reagent. Initial attempts at installing the trisubstituted alkene by uniting triflate **13** with MeLi or MeMgBr, in the presence of Ni or Pd catalyst, resulted either in recovered starting material or in erratic reactions.[8]

Iron(III)-catalysed coupling processes, which have received a considerable amount of attention recently, were also assessed, alas to no avail.[9] An unexpected solution to this problem was discovered when the Fe^{III}-catalysed reaction was performed on a sample of **13** contaminated by small amounts of ketone **14**. Whilst **13** was recovered quantitatively, **14** reacted smoothly and chemoselectively under these conditions, affording in excellent yield the long-sought-after adduct **12**. It appears, therefore, that the steric hindrance provided by the dioxolane substituent precludes any access to the vinyl triflate by the iron reagent.

At this stage, overcoming the last obstacle before the successful implementation of our strategy heavily depended upon delineating a suitable protocol that would selectively unmask the ketone function in **13** without hydrolysing the sensitive enol triflate functionality. In the event (Scheme 4), treatment of ketal **13** under our CAN-catalysed deprotection conditions (3% CAN in buffered acetonitrile, 1 hour, 60 °C), smoothly and quantitatively unveiled the carbonyl function, to afford **14** in >99% yields.[10] It is noteworthy that the acid-labile triflate moiety is untouched under these conditions.

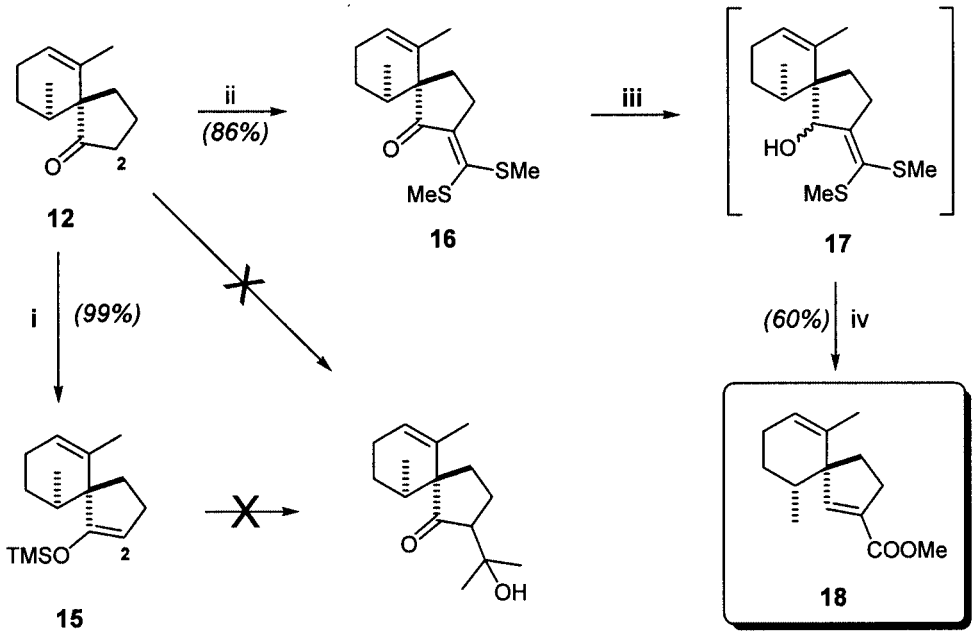
Triflate **14** was then subjected to $Fe(acac)_3$-catalysed coupling in the presence of three equivalents of methylmagnesium iodide in THF/NMP, leading exclusively to the endocyclic alkene **12** in excellent yield.[9] As already demonstrated in the seminal contributions of Cahiez et al. the remarkable chemoselectivity of iron(III)-mediated coupling reactions bodes well for future synthetic applications of this methodology.[11]

It is interesting to note that this entire sequence (enol triflate synthesis, ketal removal and Fe^{III}-catalysed coupling) can be realised sequentially without chromatographic purification of the intermediates **13** and **14**. Moreover, it can easily be performed on multigram scale, and the overall yields average 87%.

Having successfully secured large quantities of ketone **12**, we then focused our attention upon the elaboration of the five-membered ring and the introduction of the requisite appendages. Initial attempts at directly installing the isopropylol side-chain present in **3** by aldol reaction between the anion derived from ketone **12** and acetone met with failure. Subsequent efforts employing Lewis acid mediated condensations of the silyl enol ether derivative **15** with 2,2-dimethoxypropane also resulted in recovered starting material **12** (Scheme 5).

Molecular modelling studies revealed that the presence of the two α-methyl substituents provides sufficient steric hindrance around C_2 so as to preclude a proper approach of the incoming electrophile. Only the smallest reagents might be able to reach that centre. The elegant work of Junjappa et al. on the preparation and subsequent transformation of α-oxo ketene dithioketals inspired us and provided the ultimate solution to our predicament.[12]

Thus, we were delighted to observe that successive treatment of ketone **12** with KHMDS, carbon disulfide, KHMDS and finally methyl iodide led to the desired adduct **16** in 86% yield (Scheme 5). The ketone function was then chemoselectively reduced, with $NaBH_4$ in refluxing ethanol, and the crude mixture of diastereoisomeric allylic alcohols **17** was directly subjected to the action of boron trifluoride−diethyl ether in refluxing methanol for 15 hours.[12] Gratifyingly, the α,β-unsaturated ester **18** could

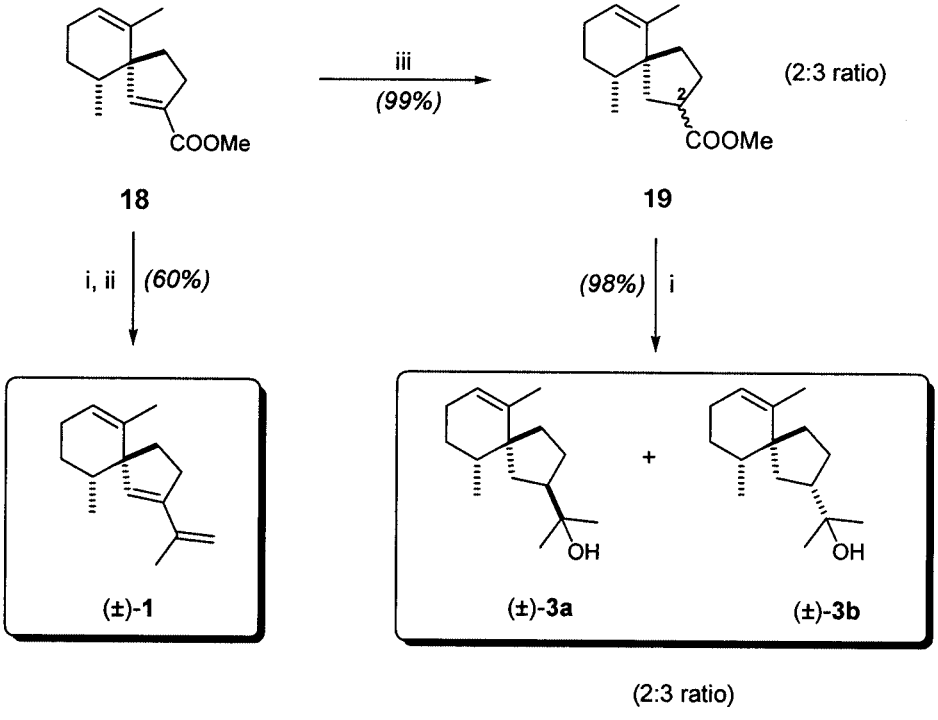


Scheme 5. Reagents and conditions: (i) lithium diisopropyl amide (LDA), TMSCl, −78 °C to room temperature; (ii) KHMDS, −78 °C, then CS_2, then KHMDS, CH_3 I; (iii) $NaBH_4$, EtOH, reflux; (iv) $BF_3{\cdot}OEt_2$, MeOH, reflux.

be isolated in 60% overall yield. This three-step sequence successfully accomplishes an impressive formal 1,2-transposition of functionality within the five-membered ring, whilst providing access to an intermediate bearing close resemblance to a broad variety of spirovetivanes.

The key intermediate **18** has already been transformed by Yamada et al. into (±)-α-vetispirene (**1**).[3b] Accordingly, treatment of unsaturated ester **18** with excess Grignard reagent in THF for 2 hours, followed directly by dehydration in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) in dry benzene, smoothly provided (±)-α-vetispirene (**1**) in an overall yield of 60% (Scheme 6).

Thus, smooth and selective reduction of substrate **18**, using magnesium in methanol, afforded the saturated ester **19** as an inseparable 2:3 mixture of C^2-epimers in quantitative yield (Scheme 6).[13] Finally, addition of methylmag-



Scheme 6. Reagents and conditions: (i) MeMgBr, 0 °C to room temperature; (ii) PTSA, benzene, 5 °C to room temperature; (iii) Mg, MeOH, 0 °C to room temperature.

nesium bromide to this mixture of stereoisomers provided (±)-agarospirol (**3a**) and (±)-hinesol (**3b**) in 98% yield (2:3 ratio).

In summary, we have shown that our condensation/spiroannulation methodology allows a ready and stereocontrolled access to three naturally occurring spirovetivanes. With our approach, the highly functionalised key intermediate **12** could be efficiently assembled in only five steps and in 54% overall yield. This precursor was subsequently transformed into (±)-agarospirol (**3a**), (±)-hinesol (**3b**) and (±)-α-vetispirene (**1**) in good overall yields.

Further efforts are now directed to the establishment of an enantioselective version of these syntheses, and towards broadening the scope and application of this connective methodology.

Experimental Section

General Remarks: Unless otherwise stated, all the reactions were carried out using anhydrous conditions and under argon. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 and 300 instruments. Chemical shifts are expressed as parts per million (ppm) down-field from tetramethylsilane or calibrated from $CDCl_3$. Mass spectra were obtained using Varian MAT-44 and Finnigan MAT-TSQ 70 spectrometers with electron impact (70 eV) and chemical ionisation (100 eV, ionisation gas: isobutane). Elemental analyses were performed in Prof. S. Laschat's analytical laboratory (Institut für Organische Chemie, Universität Stuttgart, Germany). High-resolution mass spectra were recorded in Prof. R. Flamant's laboratory (Université de Mons, Belgium).

11-Methyl-1,4-dioxaspiro[4.0.5.3]tetradecan-7-one (11a): To a solution of β-keto ketal **10a** (3.4 g, 13 mmol) in THF (75 mL) were added water (0.2 mL, 13 mmol) and potassium *tert*-butoxide (2.05 g, 18 mmol). The orange reaction mixture was stirred for 60 minutes at room temperature. Following quenching with saturated sodium hydrogen carbonate solution, the organic phase was extracted with diethyl ether, dried ($MgSO_4$), and the solvents were evaporated under reduced pressure to yield the crude spiro ketone **11a**, which was further purified by flash chromatography (silica, petroleum ether/EtOAc, 7:3) to afford pure **11a** (2.4 g, 85%) as a colourless solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3), 1.43−2.09 (m, 10 H, CH_2), 2.39−2.46 (m, 2 H, CH), 2.62−2.68 (m, 1 H, CH), 3.80−4.06 (m, 4 H, OCH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.5, 20.2, 26.1, 30.4, 31.0, 36.8, 40.7, 42.4, 62.7, 63.0, 64.2, 119.2, 211.0 ppm. MS (CI): *m/z* (%) = 225 (100) $[M + 1]^+$, 224 (10) $[M]^+$, 112 (20), 99 (20). $C_{13}H_{20}O_3$: calcd. C 69.61, H 8.99; found C 69.69, H 9.21.

10-Methyl-1-oxospiro[4.5]dec-6-en-6-yl Trifluoromethanesulfonate (14): To a solution of protected triflate **13** (110 mg, 0.31 mmol) in a mixture of acetonitrile (3 mL) and borate buffer (pH = 8.00, 3 mL), was added ceric ammonium nitrate (6 mg, 9 μmol). The yellow solution was then heated at 60 °C for 60 minutes. After cooling to room temperature, water was added, and the organic phase was extracted with dichloromethane, dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The crude triflate **14**, (95 mg, 99%) thus obtained as a colourless oil, was pure enough to be directly used in the next step. For analytical purposes, a sample was purified by flash chromatography (silica, petroleum ether/Et_2O, 10:1), affording pure triflate **14** (90 mg, 94%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH_3), 1.73−2.40 (m, 11 H, CH_2), 5.93 (td, $^3J_{H,H}$ = 4.2, $^4J_{H,H}$ = 1.2 Hz, 1 H, vinylic CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 19.6, 22.4, 25.6, 33.0, 37.8, 39.3, 55.5, 116.0, 120.2, 149.0, 216.9 ppm. MS (CI): *m/z* (%) = 313 (5) $[M + 1]^+$, 163 (30), 145 (10), 130 (10). HRMS (CI): calcd. for $C_{12}H_{15}F_3O_4S$: 313.072141; found 313.071255 $[M + 1]^+$.

6,10-Dimethylspiro[4.5]dec-6-en-1-one (12): $Fe(acac)_3$ (22 mg, 6.4 μmol) was added to a solution of triflate **14** (100 mg, 0.32 mmol) in a mixture of THF (5 mL) and NMP (3 mL). The resulting red solution was then cooled to −15 °C, and methylmagnesium iodide (0.3 mL, 3M in ether) was added dropwise. The resulting greenish suspension was stirred for 20 minutes, then water was added to quench the reaction. The organic layer was extracted with diethyl ether, dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The crude ketone **12** was then purified by flash chromatography (silica, petroleum ether/Et_2O, 10:1) to yield pure **12** (55 mg, 96%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH_3), 1.74−2.58 (m, 14 H, CH_2), 5.78 (broad s, 1 H, vinylic CH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.1, 19.4, 20.2, 22.7, 26.2, 34.7, 35.0, 39.5, 56.6, 125.5, 133.2, 221.6 ppm. MS (CI): *m/z* (%) = 179 (100) $[M + 1]^+$, 178 (55) $[M]^+$, 161 (70), 135 (25). HRMS (CI): calcd. for $C_{12}H_{18}O$: 178.135765; found 178.135772 $[M]^+$.

Acknowledgments

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