Full papers

A convenient, stereospecific synthesis of racemic juvenile hormones and some of their analogues via vinylcuprates

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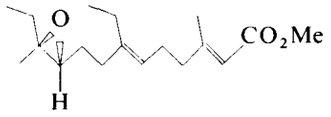
Abstract. This paper describes a stereospecific synthesis of nine 2*E*,6*E*,10(*Z*)-trienyl esters $R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{=}CH{-}(CH_2)_2{-}CR^4{=}CHCO_2Me$ (**1a-i**) and their selective conversion into the corresponding epoxides $R^1R^2C(O)CH{-}(CH_2)_2{-}CR^3{=}CH{-}(CH_2)_2{-}CR^4{=}CH{-}CO_2Me$ (**7a-i**), including the natural occurring hormones JHI–III. The trienyl system of **1** has been reached stereospecifically by allowing specifically substituted vinylcuprates, $[R^1R^2C{=}CH{-}Cu{-}Y]^{\ominus}$, to react with 4-iodo-1-butyne, followed by conversion of the formed enynes $R^1R^2C{=}CH{-}(CH_2)_2C{\equiv}CH$ (**3**) into new cuprates of the type thus $[R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{=}CH{-}Cu{-}Y]^{\ominus}$. These cuprates furnish, upon reaction with 4-iodo-1-butyne, the dienynes $R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{=}CH{-}(CH_2)_2C{\equiv}CH$ (**5**). From **5**, vinylcuprates $[R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{-}CH{-}(CH_2)_2{-}CR^4{=}CH{-}Cu{-}Y]^{\ominus}$ have been obtained which, upon reaction with carbon dioxide followed by methylation, gave compounds **1**. For the preparation of the vinylcuprates from the 1-alkynes we generally used a new alkylcopper(I) species of the type R_3Cu_2MgX. The epoxidation of **1** into **7** was performed using a literature procedure.

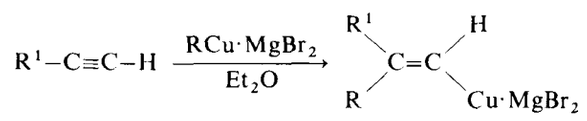
Introduction

Since the structure elucidation of the C-18 *cecropia* juvenile hormone JHI by *Röller* et al.[1], the development of stereoselective olefin syntheses has become a field of growing interest.



(JHI)

The observation that the 2*Z* and 6*Z* isomers of JHI and related compounds showed much lower biological activities than the 2*E*,6*E*-isomers emphasizes the necessity to develop synthetic methods for constructing double bonds with high stereospecificity. In 1971 a promising methodology for preparing stereospecifically substituted double bonds was reported by *Normant* et al.[2]. They observed that alkylcopper(I) compounds give *cis*-addition products with 1-alkynes in diethyl ether as solvent[3]:



In our laboratory it was found that this reaction has wider scope in the solvent tetrahydrofuran (THF)[4]. In this solvent, homocuprates, R_2CuM, react similarly with 1-alkynes; with alkylacetylenes they react even better than the $RCu{\cdot}MgBr_2$ analogues[5]. Very recently we discovered that the use of a new type of cuprate species, *viz.* R_3Cu_2MgX, is advantageous compared to that of either $RCu{\cdot}MgBr_2$ or R_2CuM for the stereospecific conversion of 1-alkynes into vinylcuprates[6]. In view of the fact that compounds such as JHI are easily accessible by selective epoxidation of the Δ^{10}-double bond of 2,6,10-trienyl esters[7], coupled with the fact that organocuprates add stereospecifically to 1-alkynes, an easy and stereospecific synthesis of JHI-like compounds, starting from simple 1-alkynes, seemed to be feasible. In a preliminary communication we have already shown that vinylcuprates readily react with 3-butynyl iodide to give the corresponding enynes, $R^1R^2C{=}CH{-}(CH_2)_2{-}C{\equiv}CH$, in excellent yields[8]. This reaction is a key step in the synthesis of the juvenile hormones JHI-III and of the analogues which are presented in this paper[9].

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[1] *H. Röller, K. H. Dahm, C. C. Sweeley* and *B. M. Trost*, Angew. Chem. **79**, 190 (1967).

[2] *J. F. Normant* and *M. Bourgain*, Tetrahedron Lett. **1971**, 2583; see also: *J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit* and *J. Villieras*, Bull. Soc. Chim. Fr. 1656 (1974).

[3] The high stereospecificity of this reaction has recently been investigated: *A. Marfat, P. R. McQuirk* and *P. Helquist*, J. Org. Chem. **44**, 3888 (1979), and references cited therein.

[4] *H. Westmijze, J. Meijer, H. J. T. Bos* and *P. Vermeer*, Recl. Trav. Chim. Pays-Bas **95**, 299 (1976).

[5] *H. Westmijze, J. Meijer, H. J. T. Bos* and *P. Vermeer, ibid.* **95**, 304 (1976).

[6] *H. Westmijze, H. Klein, J. Meijer* and *P. Vermeer, ibid.* **100**, 98 (1981).

[7] *R. J. Anderson, C. A. Henrick, J. B. Siddall* and *R. Zurflüh*, J. Am. Chem. Soc. **94**, 5379 (1972), and references cited therein.

[8] *H. Westmijze, H. Kleijn* and *P. Vermeer*, Tetrahedron Lett. **1978**, 3125.

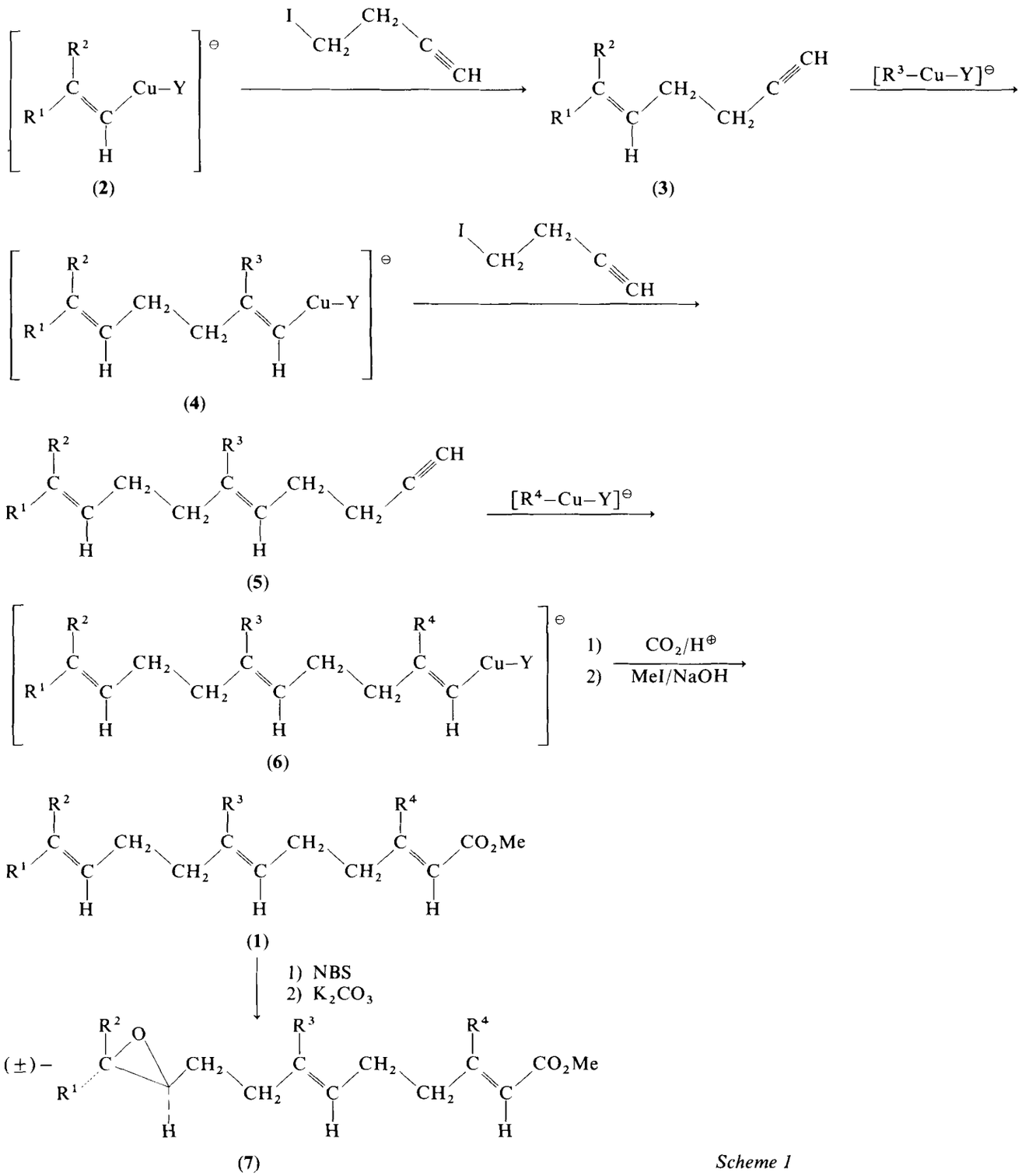
[9] See for a more laborious procedure of constructing juvenile hormone-like compounds from vinylcopper(I) compounds: *C. Chuit, G. Cahiez, J. Normant* and *J. Villieras*, Tetrahedron **32**, 1675 (1976).

Results and discussion

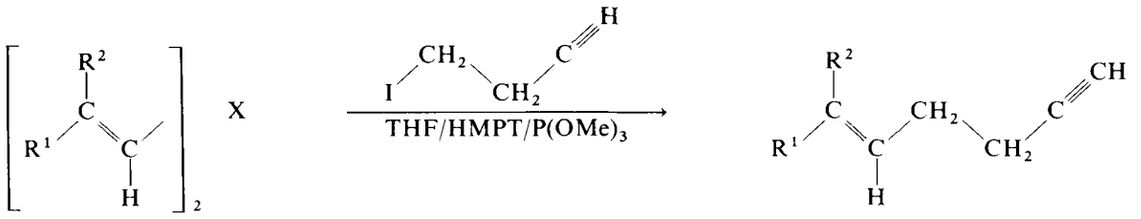
Strategy. The reaction sequence which we decided to follow for the synthesis of 2*E*,6*E*,10(*Z*)-trienyl esters **1** and the 10,11-epoxy compounds **7** is outlined in Scheme 1.
We have constructed the trienyl unit of **1** by coupling 3-butynyl iodide with suitably substituted vinylcuprates, **2** and **4**, with the conversion of vinylcuprate **6** into ester **1** as the final step. For the selective epoxidation of the Δ^{10}-double bond of **1** a satisfactory procedure, already known in the literature (*cf.* ref. 7), involves reaction of **1** with *N*-bromosuccinimide and subsequent ring closure of the resulting bromohydrin by potassium carbonate in methanol. The successive steps in this strategy will be discussed in detail in the following sections.

Preparation of enynes **3**. For our purpose two enynes of type **3** (see Scheme 1) were required. The first one, **3a** ($R^1 = R^2 = Me$), is obtained easily and in good yield (70%) by reaction of homocuprate **2a** (see Scheme 2) with two mole-equivalents of 3-butynyl iodide in a mixture of THF, hexamethylphosphoric triamide (HMPT) and trimethyl phosphite for 16 h at 25°C. The presence of HMPT and $P(OMe)_3$ during the coupling with 3-butynyl iodide is necessary in order to prevent decomposition of **2a** into $[Me_2C{=}CH{-}]_2$[9,10]. The ethyl analogue, **3b** (R^1 = Me, R^1 = Et) can be prepared as a pure isomer in 75% yield

[10] *J. F. Normant, G. Cahiez, C. Chuit* and *J. Villieras*, J. Organometal. Chem. **77**, 269 (1974).



Scheme 1



2a: $R^1 = R^2 = Me$, X = CuMgBr·2 LiBr
2b: $R^1 = Me$, $R^2 = Et$, X = Cu_2Et–MgCl·6 LiBr

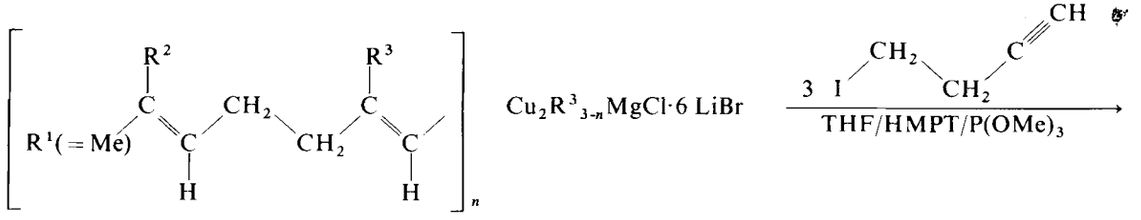
3a: $R^1 = R^2 = Me$
3b: $R^1 = Me$, $R^2 = Et$

Scheme 2

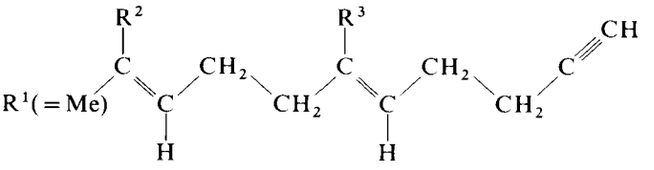
from vinylcuprate **2b** and 3 mole-equivalents of 3-butynyl iodide (see Scheme 2). Vinylcuprate **2b** is obtained from propyne and the new cuprate species $Et_3Cu_2MgCl·6$ LiBr at −25°C in THF. This result shows that, as with homocuprates such as **2a**, vinylcuprates of type **2b** can undergo a smooth reaction with 3-butynyl iodide.
Enynes **3a** and **3b** containing a terminal C–C triple bond are in principle precursors to dienynes **5**. The preparation of **5** from **3** is discussed in the next section.

Preparation of dienynes **5**. The next step in Scheme 1 involves a stereospecific synthesis of dienynes **5** from enynes **3**. We have realized this conversion in high yield (75–80%) by reaction of **3** with cuprates $R^3_3Cu_2MgCl·6$ LiBr to give vinylcuprates **4** (see Scheme 3) and by treating **4** under suitable conditions with 3-butynyl iodide. In this manner, we have prepared four dienynes, *viz.* **5a-d**, which, according to GLC and spectroscopic analysis contained only a single isomer.
For the synthesis of **5**, in which R^3 is methyl (compounds **5a** and **5b**), **3** was treated for 45 h at 0°C with one mole-equivalent of $Me_3Cu_2MgCl·6$ LiBr, *i.e.* one of the three available methyl groups of the cuprate has been used. A lower mole ratio of $Me_3Cu_2MgCl·6$ LiBr is not desirable because of substantial transfer of the vinyl group from initially formed **4a** and **4b** to the starting enyne **3** (*cf.* ref. 6).
For the synthesis of dienynes **5c** and **5d** we have used the ethylcuprate, $Et_3Cu_2MgCl·6$ LiBr. This cuprate is much more reactive than its methyl analogue. A complete conversion of **3** into **5c** and **5d** has been realized by reaction of **3** with 0.50 mole-equivalent of $Et_3Cu_2MgCl·6$ LiBr (*i.e.* two of the three available ethyl groups have been used) for 2 h at −10°C*.
Dienynes **5** already contain two of the three stereospecifically substituted double bonds of trienyl esters **1**. The presence of the terminal C–C triple bond in **5** allows a stereospecific formation of the third double bond.

Preparation of 2E,6E,10(Z)-trienyl esters **1** *and the corresponding 10,11-epoxides* **7**. For the preparation of esters **1** we first converted dienynes **5** into the vinylcuprates **6** (Scheme 4). Although compounds **1** can, in principle, be obtained in one step from **6** by reaction with ClCOOMe, it was decided to prepare **1** via their acid analogues because the sodium salts of these acids can easily be separated from the small amounts of neutral products such as $R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{=}CH{-}(CH_2)_2{-}CR^4{=}CH_2$ and $[R^1R^2C{=}CH{-}(CH_2)_2{-}CR^3{=}CH{-}(CH_2)_2{-}CR^4{=}CH{-}]_2$* concurrently formed. When prepared directly from **6**, a purification of **1** from such contaminants would probably be more laborious.
We have found that under suitably chosen reaction conditions cuprates **6** smoothly react with carbon dioxide[11]. During this reaction a sufficient amount of HMPT has to be present to prevent substantial decomposition of **6**. It further appears that for a satisfactory conversion of **6** by carbon dioxide at least 6 mole-equivalents of lithium bromide are required**. Good results are obtained when 12 mole-equivalents of this salt are present. The vinylcuprates **6**, in which R^4 is not methyl, can be obtained in one step



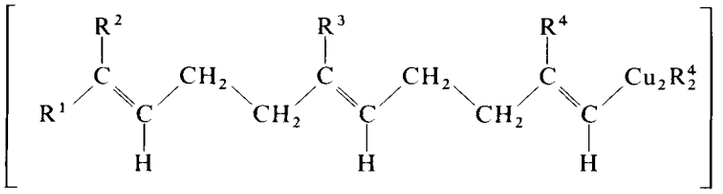
4a: $R^2 = R^3 = Me$, $n = 1$
4b: $R^2 = Et$, $R^3 = Me$, $n = 1$
4c: $R^2 = Me$, $R^3 = Et$, $n = 2$
4d: $R^2 = R^3 = Et$, $n = 2$



5a: $R^2 = R^3 = Me$
5b: $R^2 = Et$, $R^3 = Me$
5c: $R^2 = Me$, $R^3 = Et$
5d: $R^2 = R^3 = Et$

Scheme 3

* Although it is possible to transfer all ethyl groups from $Et_3Cu_2MgBr·6$ LiBr to, for example, 1-octyne (*cf.* ref. 6), we have not attempted to use all alkyl groups from the R_3Cu_2MgX species in this work.
* Arising from protolysis and thermal decomposition ("dimerization") of **6**, respectively.
** In the absence of LiBr no acid was isolated; instead compounds resulting from protonation and "dimerization" of **6** were obtained.
[11] See for the stereospecific formation of α,β-ethylenic acids from vinylcopper(I) compounds: *J. F. Normant, G. Cahiez, C. Chuit* and *J. Villieras*, J. Organometal. Chem. **77**, 281 (1974).



6a-i

MgCl·12 LiBr

1) CO_2/THF/HMPT
2) H^+
3) NaOH/MeI, $HMPT/H_2O$

1a-i ↓ **7a-i**

1, 7	R^1	R^2	R^3	R^4
a	Me	Me	Me	Me[a]
b	Me	Me	Et	Me
c	Me	Me	Et	Et
d	Me	Et	Me	Me[b]
e	Me	Et	Me	Et
f	Me	Et	Et	Me[c]
g	Me	Et	Et	Et
h	Me	Et	Et	*i*-Pr
i	Me	Et	Et	n-C_5H_{11}

[a] **7a** = JHIII
[b] **7d** = JHII
[c] **7f** = JHI

Scheme 4

from enynes **5** and $R^4_3Cu_2MgCl{\cdot}12$ LiBr. When R^4 is methyl, however, this procedure cannot be followed because of the very slow reaction of **5** with Me_3Cu_2-MgCl·12 LiBr. Even after reacting **5** for 7 days at 0°C, substantial amounts of **5** are recovered upon protolysis. In this case **6** can be more easily obtained by reacting **5** with $Me_3Cu_2MgCl{\cdot}6$ LiBr, followed by addition of 6 mole-equivalents of LiBr to the resulting vinylcuprate. It should be mentioned in this connection that we have used two mole-equivalents of $Me_3Cu_2MgCl{\cdot}6$ LiBr in these reactions in order to be sure that no transfer of the vinyl group from the resulting vinylcuprate to unreacted **5** occurs. For the other cuprates, $R^4_3Cu_2MgCl{\cdot}12$ LiBr, we have used equimolar amounts of cuprate and dienyne **5**; no experiments have been performed in which more than one R^4 group was allowed to react with **5**. The resulting acids were purified by washing their sodium salts with *n*-hexane; esterification of these acids, according to the procedure of *Shaw* et al.[12], gave trienyl esters **1** in high yield (75–80%, calculated on **5**). The purity of the nine esters **1** (for R^{1-4} see Scheme 4) obtained in this way was better than 97% according to ^{1}H NMR and GLC analysis. Trienyl esters **1f**, **1d** and **1a** are precursors to the natural hormones JHI–III (see Scheme 4). Characteristic spectroscopic data of all compounds **1** are given in the experimental section. These spectroscopic data, together with the high purity of **1** according to GLC analysis, indicate that no stereoisomers of **1** were formed during the reactions.

The selective epoxidation of the Δ^{10}-double bond in **1** is possible using the procedure described by *Henrick* et al. for the preparation of the juvenile hormone JHIII of *Hyalophora cecropia* (compound **7a**)[7]. This procedure involves electrophilic attack on **1** with *N*-bromosuccinimide (NBS) in aqueous tetrahydrofuran, followed by treatment of the resulting bromohydrin with potassium carbonate in dry methanol. The yield of this epoxidation reaction is excellent (80–90%). In compounds **1d-i** the substituents R^1 and R^2 at C(11) are different, *viz.* Me and Et, respectively. During the epoxidation reaction of **1d-i** the *cis* orientation of R^1 and the hydrogen atom at C(10) is retained in the product. During the conversion of **4d** into **7d**, this retention of configuration follows from ^{1}H NMR analysis which shows that our compound **7d** is identical with juvenile hormone JHII in which the methyl group at C(11) and the hydrogen atom at C(10) are *cis* oriented[7]. As for as **7e-i** are concerned, the *cis* orientation of R^1 and H at C(10) is concluded from the fact that, just as is found for **7d**, the methyl group R^1 gives a sharp signal in the narrow range δ 1.18–1.19 in the ^{1}H NMR spectrum (see Experimental section). For the corresponding *trans* epoxides the methyl signal is expected at δ 1.21–1.22 (compare δ 1.21–1.22 found for **7a-c** with R^2 = Me and δ 1.18–1.19 found when R^1 = Me). In the ^{1}H NMR spectra of **7d-i**, however, the methyl signal at δ 1.21–1.22 is absent. Using the above procedure the epoxidation of **1** leads to racemic epoxides. The absolute configuration of natural JHI has been elucidated by *Nakanishi* et al.[13a] and by *Faulkner* et al.[13b]. They found that this natural hormone possesses the 10*R*,11*S*-configuration. Bioassay results, however, indicated that in the case of JHI the synthetic racemate exhibits activities of similar magnitude to those of the natural, optically active hormone[14]. The configurations of the two double bonds and of the epoxide ring of this compound, on the other hand, influence its biological activity considerably; the highest activity has been found for the compound with a *cis*-10,11-epoxy ring and with both Δ^2- and Δ^6-double bonds in the *E*-configuration[14].
The biological activity of our compounds is presently under investigation*.

Conclusion

Our method of obtaining racemic juvenile hormones and analogues with the required configurations of the two double bonds and the epoxide ring via a stereospecific synthesis of the 2*E*,6*E*,10(*Z*)-trienyl esters **1** is straightforward. The crucial role played by vinylcuprates in this methodology emphazises the synthetic utility of these reagents. The present work opens new perspectives for the synthesis of many other terpenes and terpene-like compounds.

* This work is being performed in cooperation with Dr. *H. W. A. Biessels* of our laboratory.

[12] *J. E. Shaw, D. C. Kunerth* and *J. J. Sherry*, Tetrahedron Lett. 689 (1973).
[13a] *K. Nakanishi, D. A. Schooley, M. Koreeda* and *J. Dillon*, J. Chem. Soc., Chem. Commun. 1235 (1971).
[b] *D. J. Faulkner* and *M. R. Petersen*, J. Am. Chem. Soc. **93**, 3766 (1971).
[14] *K. H. Dahm, B. M. Trost* and *H. Röller*, J. Am. Chem. Soc. **89**, 5292 (1967).

Experimental section

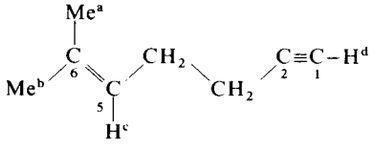
All operations were performed in an atmosphere of dry nitrogen. ^{1}H NMR spectra were determined on a Varian EM-390 spectrometer using CCl_4 as solvent and Me_4Si (δ 0 ppm) as internal standard. ^{13}C NMR spectra were determined on a Varian CFT-20 spectrometer using $CDCl_3$ as solvent and Me_4Si (δ 0 ppm) as internal standard. IR spectra were recorded on a Perkin-Elmer 457 spectrometer. GLC analyses were carried out on Pye-104 chromatograph (conditions SE33, 10% on Chromosorb W).

Materials

THF was distilled from $LiAlH_4$. Copper(I) bromide and copper(I) chloride were obtained using the procedure of *Keller* and *Wycoff*[15]. The alkyl reagents were prepared in THF from the corresponding alkyl chlorides and magnesium (Merck–Schuchardt). Their molarity was determined by titration with *sec*-butanol according to the procedure of *Watson*[16]. HMPT was dried using lithium[17]. Trimethyl phosphite was obtained from Fluka AG. Lithium bromide was dried at 220°C in high vacuum and was used as a 2.0 or 3.0 M solution in THF.
3-Butynyl iodide was obtained by treating the tosylate $HC{\equiv}C(CH_2)_2{-}OTos$ with NaI in acetone[18].

Preparation of 6-methyl-5-hepten-1-yne (**3a**)

A solution of $Me_2C{=}CH{-}MgBr$ (0.120 mole) in THF (150 ml) was added cautiously at −60°C to −50°C to a stirred solution of CuBr·2 LiBr (0.060 mole) in THF (60 ml). After stirring for 15 min. at −60°C HMPT (50 ml), $P(OMe)_3$ (50 ml) and 3-butynyl iodide (0.120 mole) were successively added. The temperature of the resulting reaction mixture was allowed to rise to 25°C and stirring at this temperature was continued for 16 h. The reaction mixture was then poured into an aqueous HCl solution (2 N, 400 ml) and the product was isolated by extraction with pentane (3 × 75 ml). The combined extracts were washed with 2 N HCl (3 × 300 ml) and dried over $MgSO_4$. The solvent was distilled off and the residue was purified from some unreacted 3-butynyl iodide by column chromatography (Al_2O_3- 5% H_2O/*n*-pentane).
Compound **3a** (yield: 70%, calculated on $Me_2C{=}CH{-}MgBr$), thus obtained, could be used without further purification for the preparation of **5***. Physical constants of **3a**: b.p. 60–61°C/60 mm Hg; n_D^{20} 1.4447. Characteristic spectroscopic data of



(**3a**):

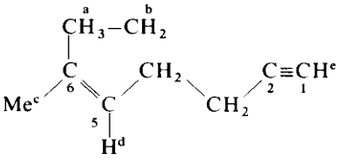
^{1}H NMR (30% (v/v) solution in CCl_4): δ: 1.60 (Me^a), 1.68 (Me^b), 5.12 (H^c), 2.0–2.3 (2 × CH_2), 1.72 (H^d).
^{13}C NMR: δ 67.90 (C^1), 83.94 (C^2), 122.48 (C^5), 132.50 (C^6).
IR (film): 3310, 2118 cm^{-1}.

Preparation of (Z)-6-methyl-5-octen-1-yne (**3b**)

A solution of EtMgCl (0.150 mole) in THF (100 ml) was added cautiously at −60° to −50°C to a stirred solution of CuBr·3 LiBr (0.100 mole) in THF (100 ml). After the addition was completed, stirring was continued for 15 min. at −60°C. Excess liquified propyne (0.250 mole) was then immediately added and the temperature of the resulting mixture allowed to rise to −25°C. The mixture was kept at this temperature for 2 h with stirring. Subsequently, the temperature was lowered to −60°C and HMPT (50 ml), $P(OMe)_3$ (50 ml) and 3-butynyl iodide (0.150 mole) were successively added. The reaction mixture was then stirred for 16 h at 25°C. Product **3b** was isolated and purified from some unreacted 3-butynyl iodide as described for **3a**; yield of **3b**: 75% (based on transfer of two Et groups from $Et_3Cu_2MgCl{\cdot}6$ LiBr to propyne).
Physical constants of **3b**: b.p. 78–80°C/75 mm Hg; n_D^{20} 1.4478.

* Undistilled **3a** contained some $Me_2C{=}CH{-}CH{=}CMe_2$ which was formed during the synthesis of $Me_2C{=}CHMgBr$. This 1,3-diene was easily removed in the next step.

Characteristic spectroscopic data of

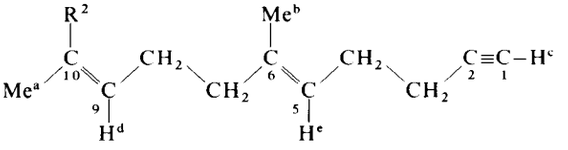


(**3b**):

^{1}H NMR (30% (v/v) solution in CCl_4): δ 0.96 ($CH_3{}^a$), 2.03 ($CH_2{}^b$), 1.68 (Me^c), 5.12 (H^d), 2.0–2.3 (2 × CH_2), 1.78 (H^e).
^{13}C NMR: δ 67.98 (C^1), 84.14 (C^2), 122.08 (C^5), 138.53 (C^6).
IR (film): 3310, 2127 cm^{-1}.

Preparation of 6,10-dimethyl-5,9-alkadien-1-ynes **5a** *and* **5b**

A solution of MeMgCl (0.120 mole) in THF (110 ml) was added cautiously at 0° to −10°C to a stirred solution of CuBr·3 LiBr (0.080 mole) in THF (120 ml). After the addition of the Grignard reagent the reaction mixture was stirred for 15 min. at 0°C. To the cuprate, thus obtained, was added enyne **3** (0.040 mole). The resulting mixture was stirred for 45 h at −2°–0°C. The temperature of the reaction mixture was then lowered to −15°C and HMPT (40 ml), $P(OMe)_3$ (40 ml) and 3-butynyl iodide (0.120 mole) were successively added. Stirring of the reaction mixture was then continued for 16 h at 25°C. The dienynes **5a** and **5b** were isolated and purified as described for **3a**; yield of **5a** and **5b**: 80% (calculated on **3**).
Compound **5a**: b.p. 55–57°C/0.05 mm Hg, n_D^{20} 1.4718;
Compound **5b**: b.p. 70–72°C/0.05 mm Hg, n_D^{20} 1.4733.
Characteristic spectroscopic data of



(**5a**: R^2 = Me; **5b**: R^2 = CH_3CH_2)

5a: ^{1}H NMR (30% (v/v) solution in CCl_4): δ 1.58 (Me^b + R^2), 1.64 (Me^a), 1.72 (H^c), 1.8–2.3 (4 × CH_2), 4.9–5.3 (H^d + H^e).
^{13}C NMR: δ 67.95 (C^1), 84.36 (C^2), 122.37 + 124.12 (C^5 + C^9), 131.19 (C^{10}), 136.56 (C^6).
IR (film): 3318, 2120 cm^{-1}.

5b: ^{1}H NMR (30% (v/v) solution in CCl_4): δ 0.94 (Me of R^2), 1.60 (Me^b), 1.63 (Me^a), 1.72 (H^c), 1.8–2.3 (5 × CH_2), 4.8–5.3 (H^d + H^e).
^{13}C NMR: δ 67.95 (C^1), 84.21 (C^2), 122.35 + 123.67 (C^5 + C^9), 136.42 and 136.85 (C^6 + C^{10}).
IR (film): 3308, 2118 cm^{-1}.

Preparation of 6-ethyl-10-methyl-5,9-alkadien-1-ynes **5c** *and* **5d**

A solution of EtMgCl (0.090 mole) in THF (65 ml) was added cautiously at −60°C to −50°C to a stirred solution of CuBr·3 LiBr (0.060 mole) in THF (120 ml). After the addition of the Grignard reagent the resulting mixture was stirred for 15 min. at −60°C. Subsequently, enyne **3** (0.060 mole) was added. After stirring the resulting reaction mixture for 2 h at −10°C the temperature of the mixture was lowered to −60°C and HMPT (30 ml), $P(OMe)_3$ (30 ml) and 3-butynyl iodide (0.090 mole) were successively added. Stirring was then continued for 16 h at 25°C. Compounds **5c** and **5d**, thus formed, were isolated and purified as described for **3a**; yield of **5c-d**: 80% (calculated on **3**).
Compound **5c**: b.p. 67–69°C/0.01 mm Hg, n_D^{20} 1.4700;
Compound **5d**: b.p. 76–80°C/0.01 mm Hg, n_D^{20} 1.4727.

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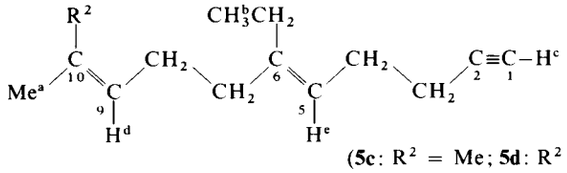
[16] *S. C. Watson* and *J. F. Eastham*, J. Organometal. Chem. **9**, 165 (1967).
[17] *L. Brandsma*, "Preparative Acetylenic Chemistry", Elsevier, Amsterdam 1971.
[18] *G. Eglinton* and *M. C. Whiting*, J. Chem. Soc. 3650 (1950).

Characteristic spectroscopic data of



(**5c**: R^2 = Me; **5d**: R^2 = Et)

5c: ^{1}H NMR (30% (v/v) solution in CCl_4): δ 0.97 (Me^b), 1.58 (R^2 = Me), 1.65 (Me^a), 1.75 (H^c), 1.8–2.3 (5 × CH_2), 4.9–5.3 (H^d + H^e).
^{13}C NMR: δ 68.39 (C^1), 84.25 (C^2), 122.35 + 124.60 (C^5 + C^9), 131.11 (C^{10}), 142.50 (C^6).
IR (film): 3318, 2122 cm^{-1}.

5d: ^{1}H NMR (30% (v/v) solution in CCl_4): δ 0.94 (Me^b + Me of R^2), 1.64 (Me^a), 1.73 (H^c), 1.8–2.3 (6 × CH_2), 4.9–5.2 (H^d + H^e).
^{13}C NMR: δ 67.99 (C^1), 84.05 (C^2), 121.91 + 123.81 (C^5 + C^9), 136.68 (C^{10}), 142.26 (C^6).
IR (film): 3308, 2122 cm^{-1}.

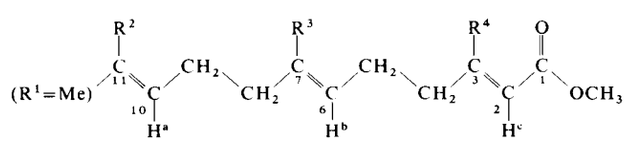
Preparation of methyl 3,7,11-trialkyl-2,6,10-alkatrienoates **1a-i**

a) R^4 in 1 is methyl

A solution of MeMgCl (0.030 mole) in THF (30 ml) was added cautiously at −10° to 0°C to a stirred solution of CuBr·3 LiBr (0.020 mole) in THF (30 ml). To complete the formation of the cuprate, stirring of the reaction mixture was continued for 15 min. at 0°C. After this period enyne **5** (0.005 mole) was added and the resulting reaction mixture stirred for 45 h at 0°C. Subsequently, lithium bromide (0.060 mole) in THF (20 ml) and HMPT (10 ml) were added successively to the reaction mixture at −10°C. The formation of the desired acids was achieved by bubbling dry carbon dioxide (50 ml/min.) through the solution for 1 h at 25°C. The resulting acids were isolated by pouring the reaction mixture into 2 N HCl (100 ml) and extracting with diethyl ether (2 × 75 ml). After washing the combined extracts with 2 N HCl (2 × 50 ml), the solvent was removed *in vacuo*. The crude acids, thus obtained, were purified from apolar material by adding them to a solution of NaOH (0.040 mole) in a mixture of HMPT (50 ml) and H_2O (10 ml), shaking the resulting solutions for 15 min. at 25°C and treating these solutions twice with 30 ml of n-hexane. The n-hexane layers containing some apolar material were decanted and excess MeI (0.077 mole) was added to the HMPT/H_2O layer. The resulting reaction mixture was then shaken for 30 min. at 25°C. Subsequently, the mixture was poured into 0.6 N HCl (100 ml) and the trienyl esters were extracted with Et_2O/n-pentane (80/20 (v/v), 3 × 30 ml). The combined extracts were washed with water (3 × 25 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give colourless trienyl esters **1** in 75–80% yield (calculated on **5**). According to GLC and ^{1}H NMR analyses the purity of the isolated trienyl esters was at least 97% and no further purification prior to conversion into epoxides **7** was necessary.

b) R^4 in 1 is Et, i-Pr, or *n*-Pentyl

A solution of R^4MgCl (0.015 mole, R^4 = Et, i-Pr, or *n*-C_5H_{11}) in THF (15 ml) was added cautiously to a stirred solution of CuCl·6 LiBr (0.010 mole) in THF (20 ml) at −60°C to −50°C. After 15 min. dienyne **5** (0.005 mole) was added at −60°C, and the resulting mixture stirred for 2 h at 0°C. The reaction mixture was cooled to −50°C and HMPT (5 ml) added. Dry carbon dioxide was then bubbled through the reaction mixture for 1 h at 25°C (rate: 50 ml/min). The subsequent procedure was identical to that described under **a)**. Yield of the colourless trienyl esters **1**: 80–85% (calculated on **5**); purity ≥97% (based on ^{1}H NMR and GLC analyses).
Characteristic data found for the trienyl esters **1a-i***:



* The ^{1}H NMR spectra were recorded from solutions of **1** in CCl_4 (30% (v/v)).

Compound **1a**: [R^2 = R^3 = R^4 = Me]: n_D^{20} 1.4876
^{1}H NMR: δ 1.57 (R^2 + R^3), 1.64 (R^1), 1.85–2.30 (4 × CH_2), 2.10 (R^4), 3.60 (OCH_3), 4.9–5.3 (H^a + H^b), 5.58 (H^c).
^{13}C NMR: 167.06 (C^1), 159.87 (C^3), 136.01 (C^7), 131.18 (C^{11}), 124.09 (C^{10}), 122.74 (C^6), 115.14 (C^2).
IR (film): 1720, 1648 cm^{-1}.

Compound **1b**: [R^2 = R^4 = Me, R^3 = Et]: n_D^{20} 1.4861
^{1}H NMR: δ 0.93 (Me group of R^3), 1.56 (R^2), 1.63 (R^1), 2.00 (CH_2 group of R^3), 1.85–2.30 (4 × CH_2), 2.12 (R^4), 3.60 (OCH_3), 4.84–5.20 (H^a + H^b), 5.59 (H^c).
^{13}C NMR: 166.95 (C^1), 159.78 (C^3), 141.82 (C^7), 131.03 (C^{11}), 124.16 (C^{10}), 122.21 (C^6), 115.07 (C^2).
IR (film): 1721, 1650 cm^{-1}.

Compound **1c**: [R^2 = Me, R^3 = R^4 = Et]: n_D^{20} 1.4836
^{1}H NMR: δ 0.94 (Me group of R^3), 1.04 (Me group of R^4), 1.57 (R^2), 1.63 (R^1), 2.02 (CH_2 of R^3), 2.60 (CH_2 of R^4), 3.60 (OCH_3), 4.85–5.20 (H^a + H^b), 5.64 (H^c), 1.85–2.30 (4 × CH_2).
^{13}C NMR: 166.54 (C^1), 165.56 (C^3), 141.73 (C^7), 130.99 (C^{11}), 124.16 (C^{10}), 122.35 (C^6), 114.29 (C^2).
IR (film): 1720, 1643 cm^{-1}.

Compound **1d**: [R^2 = Et, R^3 = R^4 = Me]: n_D^{20} 1.4860
^{1}H NMR: δ 0.92 (Me of R^2), 1.59 (R^3), 1.63 (R^1), 2.00 (CH_2 of R^2), 1.85–2.30 (4 × CH_2), 2.12 (R^4), 3.60 (OCH_3), 4.85–5.20 (H^a + H^b), 5.58 (H^c).
^{13}C NMR: 166.83 (C^1), 159.66 (C^3), 136.75 and 135.79 (C^7 and C^{11}), 123.57 (C^{10}), 122.64 (C^6), 115.03 (C^2).
IR (film): 1721, 1650 cm^{-1}.

Compound **1e**: [R^2 = R^4 = Et, R^3 = Me]: n_D^{20} 1.4847
^{1}H NMR: δ 0.93 (Me of R^2), 1.03 (Me of R^4), 1.59 (R^3), 1.63 (R^1), 2.00 (CH_2 of R^2), 1.80–2.30 (4 × CH_2), 2.60 (CH_2 of R^4), 3.61 (OCH_3), 4.85–5.20 (H^a + H^b), 5.52 (H^c).
^{13}C NMR: 166.39 (C^1), 165.42 (C^3), 136.70 and 135.71 (C^7 and C^{11}), 123.57 (C^{10}), 122.77 (C^6), 114.23 (C^2).
IR (film): 1718, 1642 cm^{-1}.

Compound **1f**: [R^2 = R^3 = Et, R^4 = Me]: n_D^{20} 1.4878
^{1}H NMR: δ 0.94 (Me of R^2 + Me of R^3), 1.63 (R^1), 1.80–2.30 (6 × CH_2), 2.13 (R^4), 3.60 (OCH_3), 4.83–5.20 (H^a + H^b), 5.58 (H^c).
^{13}C NMR: 166.25 (C^1), 159.02 (C^3), 141.38 (C^7), 136.26 (C^{11}), 123.53 (C^{10}), 122.05 (C^6), 114.88 (C^2).
IR (film): 1720, 1648 cm^{-1}.

Compound **1g**: [R^2 = R^3 = R^4 = Et]: n_D^{20} 1.4850
^{1}H NMR: δ 0.94 (CH_3 of R^2 + CH_3 of R^3), 1.02 (CH_3 of R^4), 1.63 (R^1), 1.80–2.30 (6 × CH_2), 2.60 (CH_2 of R^4), 3.60 (OCH_3), 4.85–5.30 (H^a + H^b), 5.56 (H^c).
^{13}C NMR: 166.51 (C^1), 165.49 (C^3), 141.70 (C^7), 136.73 (C^{11}), 123.74 (C^{10}), 122.32 (C^6), 114.26 (C^2).
IR (film): 1720, 1642 cm^{-1}.

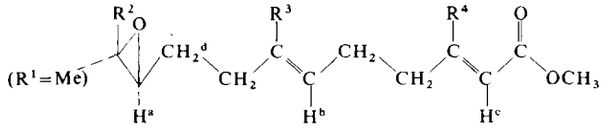
Compound **1h**: [R^2 = R^3 = Et, R^4 = i-Pr]: n_D^{20} 1.4837
^{1}H NMR: δ 0.95 (CH_3 of R^2 + CH_3 of R^3), 1.02 (2 × CH_3 of R^4), 1.63 (R^1), 1.80–2.30 (6 × CH_2), 3.60 (OCH_3), 4.04 (>C*H* of R^4), 4.80–5.22 (H^a + H^b), 5.50 (H^c).
^{13}C NMR: 168.29 and 166.37 (C^1 + C^3), 141.44 (C^7), 136.55 (C^{11}), 123.70 (C^{10}), 122.53 (C^6), 113.51 (C^2).
IR (film): 1720, 1637 cm^{-1}.

Compound **1i**: [R^2 = R^3 = Et, R^4 = n-C_5H_{11}]: n_D^{20} 1.4807

^{1}H NMR: δ 0.87 (CH_3 of R^4), 0.93 (CH_3 of R^2 + CH_3 of R^3), 1.10–1.53 (3 × CH_2 of R^4), 1.63 (R^1), 1.80–2.30 (6 × CH_2) 2.58 (1 × CH_2 of R^4), 3.59 (OCH_3), 4.85–5.20 (H^a + H^b), 5.54 (H^c).
^{13}C NMR: 166.65 (C^1), 164.31 (C^3), 141.67 (C^7), 136.69 (C^{11}), 123.75 (C^{10}), 122.34 (C^6), 114.66 (C^2).
IR (film): 1720, 1642 cm^{-1}.

Preparation of racemic methyl 3,7,11-trialkyl-10,11-epoxy-2,6--alkadienoates **7a-i**

For the epoxidation of **1a-i** into **7a-i** we followed the procedure described by *Henrick* et al. for the conversion of trienyl ester **1a** into its epoxide **7a**[7]. In our case the epoxidation of **1** was performed on 0.003 mole scale. The crude epoxides **7a-i** were obtained in 80–90% yield. According to ^{1}H NMR analysis these crude epoxides appeared to be reasonably pure (≥90%). In all cases samples of **7** were subjected to column chromatography on silica gel (100 Mesh/Mallinckrodt; elution with *n*-hexane/Et_2O (90/10 v/v)). The measured refractive indices refer to these purified samples. During this purification step considerable loss of material occurred but we did not investigate conditions further to prevent this.
Characteristic data found for epoxides **7a-i***:



Compound **7a**: (R^2 = R^3 = R^4 = Me): n_D^{20} 1.4799

^{1}H NMR: δ 1.19 (R^1), 1.21 (R^2), 1.60 (R^3), 1.30–1.70 (H^d), 1.80–2.30 (3 × CH_2), 2.12 (R^4), 2.48 (H^a), 3.60 (OCH_3), 5.12 (H^b), 5.58 (H^c).
IR (film): 1720, 1650 cm^{-1}.

Compound **7b**: (R^2 = R^4 = Me, R^3 = Et): n_D^{20} 1.4803

^{1}H NMR: δ 0.94 (Me of R^3), 1.18 (R^1), 1.21 (R^2), 1.30–1.70 (H^d), 1.80–2.30 (4 × CH_2), 2.13 (R^4), 2.48 (H^a), 3.60 (OCH_3), 5.07 (H^b), 5.58 (H^c).
IR (film): 1720, 1648 cm^{-1}.

Compound **7c**: (R^2 = Me, R^3 = R^4 = Et): n_D^{20} 1.4785

^{1}H NMR: δ 0.94 (CH_3 of R^3), 1.04 (CH_3 of R^4), 1.19 (R^1), 1.22 (R^2), 1.30–1.70 (H^d), 1.80–2.30 (4 × CH_2), 2.49 (H^a), 2.59 (CH_2 of R^4), 3.60 (OCH_3), 5.09 (H^b), 5.52 (H^c).
IR (film): 1721, 1642 cm^{-1}.

* The ^{1}H NMR spectra were recorded from solutions of **7** in CCl_4 (20% (v/v)).

Compound **7d**: (R^2 = Et; R^3 = R^4 = Me): n_D^{20} 1.4802

^{1}H NMR: δ 0.94 (CH_3 of R^2), 1.18 (R^1), 1.30–1.70 (H^d), 1.60 (R^3), 1.80–2.30 (4 × CH_2), 2.12 (R^4), 2.50 (H^a), 3.60 (OCH_3), 5.10 (H^b), 5.55 (H^c).
IR (film): 1720, 1647 cm^{-1}.

Compound **7e**: (R^2 = R^4 = Et, R^3 = Me): n_D^{20} 1.4797

^{1}H NMR: δ 0.97 (CH_3 of R^2), 1.04 (CH_3 of R^4), 1.18 (R^1), 1.30–1.68 (H^d + CH_2 of R^2), 1.62 (R^3), 1.95–2.25 (3 × CH_2), 2.50 (H^a), 2.60 (CH_2 of R^4), 3.61 (OCH_3), 5.12 (H^b), 5.53 (H^c).
IR (film): 1720, 1645 cm^{-1}.

Compound **7f**: (R^2 = R^3 = Et, R^4 = Me): n_D^{20} 1.4803

^{1}H NMR: δ 0.95 (CH_3 of R^2 + CH_3 of R^3), 1.18 (R^1), 1.30–1.70 (H^d + CH_2 of R^2), 1.80–2.30 (4 × CH_2), 2.12 (R^4), 2.50 (H^a), 3.60 (OCH_3), 5.08 (H^b), 5.57 (H^c).
IR (film): 1720, 1647 cm^{-1}.

Compound **7g**: (R^2 = R^3 = R^4 = Et): n_D^{20} 1.4791

^{1}H NMR: δ 0.96 (CH_3 of R^2 + CH_3 of R^3), 1.02 (CH_3 of R^4), 1.18 (R^1), 1.30–1.70 (H^d + CH_2 of R^2), 1.80–2.30 (4 × CH_2), 2.50 (H^a), 2.58 (CH_2 of R^4), 3.61 (OCH_3), 5.08 (H^b), 5.53 (H^c).
IR (film): 1720, 1642 cm^{-1}.

Compound **7h**: (R^2 = R^3 = Et; R^4 = i-Pr): n_D^{20} 1.4784

^{1}H NMR: δ 0.97 (CH_3 of R^2 + CH_3 of R^3), 1.01 (2 × CH_3 of R^4), 1.19 (R^1), 1.30–1.70 (H^d + CH_2 of R^2), 1.80–2.30 (4 × CH_2), 2.53 (H^a), 3.61 (OCH_3), 4.02 (>C*H* of R^4), 5.10 (H^b), 5.52 (H^c).
IR (film): 1720, 1638 cm^{-1}.

Compound **7i**: (R^2 = R^3 = Et, R^4 = *n*-C_5H_{11}): n_D^{20} 1.4769

^{1}H NMR: δ 0.88 (CH_3 of R^4), 0.96 (CH_3 of R^2 + CH_3 of R^3), 1.18 (R^1), 1.10–1.70 (H^d + CH_2 of R^2 + 3 × CH_2 of R^4), 1.80–2.30 (4 × CH_2), 2.50 (H^a), 2.58 (CH_2 of R^4)[l] 3.60 (OCH_3), 5.08 (H^b), 5.54 (H^c).
IR (film): 1720, 1642 cm^{-1}.

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