DOI: 10.1002/ejoc.200800936

# A Convenient Approach to Polycyclic Derivatives with a *cis*-Fused 2,6-Dioxabicyclo[4.3.0]nonane System by the Sequence Ring-Opening/ Intramolecular Ring-Closing Enyne Metathesis/Diels–Alder Reaction

**Ana Aljarilla,[a] Maria C. Murcia,[a] Aurelio G. Csákÿ,[a] and Joaquín Plumet*[a]**

*Dedicated to Professor Rosa Fernández of the University of Oviedo*

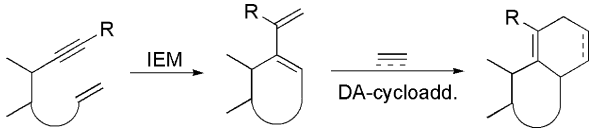
**Keywords:** Metathesis / Cycloaddition / Diels–Alder reaction / Ruthenium / Polycycles

7-Oxanorbornene derivatives functionalized with alkyne appendages undergo intramolecular enyne metathesis reactions to give *cis*-fused 2,6-dioxabicyclo[4.3.0]nonane derivatives. These compounds have a diene functionality that allows their reaction with dienophiles (*N*-phenylmaleimide) to yield densely functionalized polycyclic compounds.
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

## Introduction

Nowadays, olefin metathesis is a standard method for the formation of C–C bonds.[1] Because the three main types of metathesis reactions, that is, ring-opening metathesis (ROM), ring-closing metathesis (RCM) and cross metathesis (CM), allow the synthesis of complex molecules, they are now widely used in an almost routine fashion.[2]

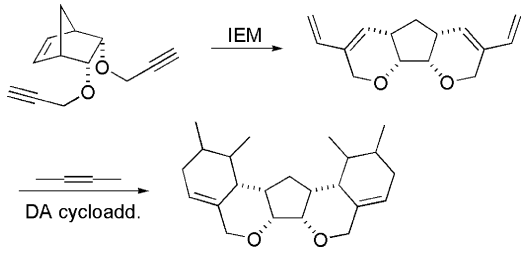
In the case of intramolecular enyne metathesis reactions[3] (IEM, Scheme 1), the final product is an exocyclic 1,3-diene that can be further transformed into polycyclic structures through Diels–Alder cycloaddition reactions.




Scheme 1. The intramolecular enyne metathesis (IEM)/Diels–Alder cycloaddition sequence.

Since the first reports of diene synthesis by enyne metathesis,[4] this methodology has been lavishly applied in organic synthesis. For instance, the construction of very different types of complex carbo- and heterocyclic compounds has been reported, including conformational constrained amino acids,[5] polycyclic β-lactams[6] and *C*-glycosides or other sugar derivatives,[7] among many other molecular architectures.[8] From a methodological point of view, this procedure is also a valuable alternative to the transformation of carbohydrates into carbocycles.[9] Moreover, many kinds of dienophilic components have been used, including singlet oxygen[10] and fullerene $C_{60}$.[11]

Norbornene derivatives have been used as convenient substrates in metathesis reactions because the release of ring-strain during the metathesis process (in particular those that include ROM reactions) makes the reaction essentially irreversible.[12] For this reason norbornene derivatives are valuable monomers in ring-opening metathesis polymerization (ROMP) reactions.[13] Also, bis-propargylic norbornene derivatives have been used as starting materials for the construction of pentacyclic ring systems by the IEM/DA reaction sequence (Scheme 2).[14]



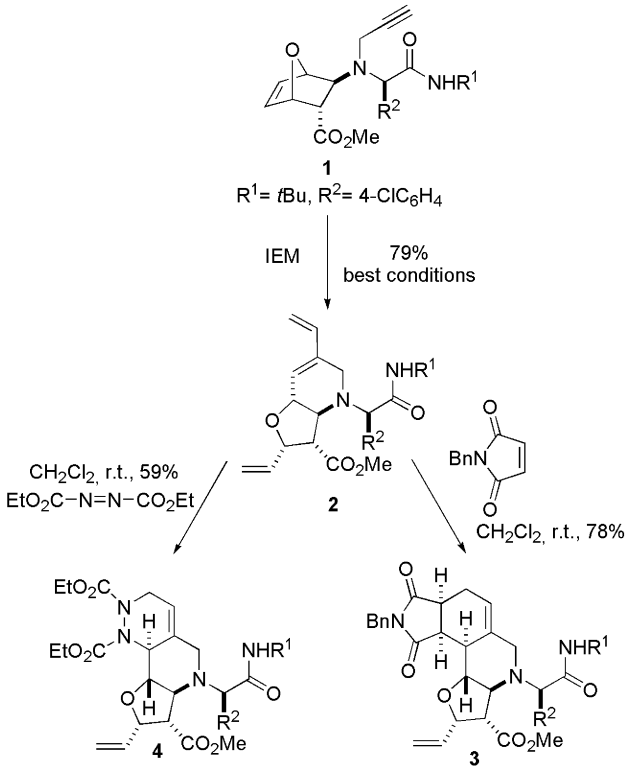

Scheme 2. The intramolecular enyne metathesis/Diels–Alder cycloaddition sequence for norbornene derivatives.

However, it is surprising that, to the best of our knowledge, in the case of the related 7-oxanorbornene derivatives,[15] with the exception of one isolated report,[16] this process has not yet been explored. In this case the oxabicyclic amino acid derivative **1** was transformed into bicyclic compounds **2** through the IEM protocol. Further reac-

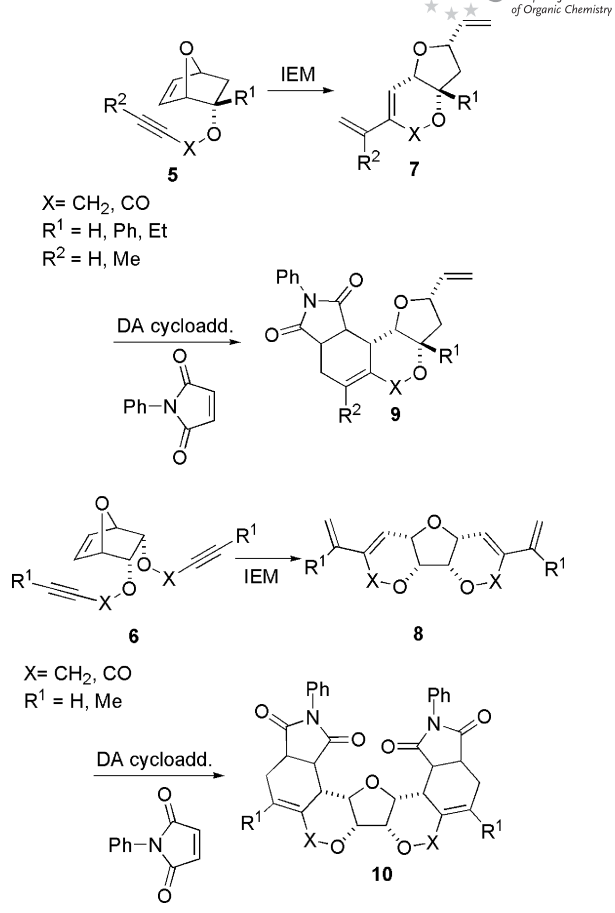
[a] Universidad Complutense, Facultad de Química, Departamento de Química Orgánica,
28040 Madrid, Spain
Fax: 34-91-3944231
E-mail: plumety@quim.ucm.es
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.


WILEY InterScience DISCOVER SOMETHING GREAT
© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

tion of **2** with *N*-benzylmaleimide or diethyl azodicarboxylate afforded tetra- **3** or tricyclic **4** derivatives, respectively (Scheme 3).




Scheme 3. The intramolecular enyne metathesis/Diels–Alder cycloaddition sequence for an oxanorbornene derivative (see ref.[16]).




Scheme 4. The intramolecular enyne metathesis/Diels–Alder cycloaddition sequence for 2-mono- and 2,3-disubstituted derivatives of 7-oxanorbornenes **5** and **6**.

On the basis of these previous reports, we thought that the IEM reactions of the mono- and 2,3-disubstituted derivatives of the 7-oxabicyclo[2.2.1]hept-5-ene framework **5** and **6** (Scheme 4) should give bi- and tricyclic dienic compounds **7** and **8**, respectively. Subsequent DA reactions of **7** and **8** with the appropriate dienophile should pave the way for the preparation of the densely functionalized polycyclic compounds **9** and **10**.

Note that the central cores of these compounds are a fused *cis*-2,6-dioxabicyclo[4.3.0]nonane skeleton, a motif widely distributed in nature. For instance, compounds such as dysiherbaine **11a** and neodysiherbaine **11b** (Figure 1) are excitatory amino acids with potent convulsant activity.[17] On the other hand, some pyranonaphthoquinone antibiotics,[18] such as kalafungin **12a**, frenolicin **12b** and arizomicin **12c** (Figure 1), bear the naphtho[2,3-*c*]pyran-5,10-dione substructure as the basic skeleton. These compounds exhibit activity against a variety of Gram-positive bacteria, pathogenic fungi and yeasts as well as antiviral activity. Finally some furanopyrones of the styryl lactone family,[19] such as altholactone **13a** and isoaltholactone **13b**, possess, among others, interesting antitumour properties. Therefore compounds **9** and **10** may be considered as potentially useful derivatives of this basic skeleton.

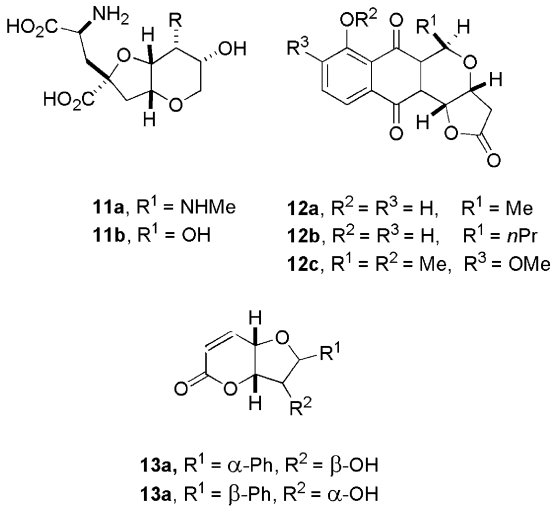



Figure 1. Some natural products containing the *cis*-2,6-dioxabicyclo[4.3.0]nonane skeleton.

In this report we wish to describe our efforts towards the synthesis of compounds **7**–**10** (Scheme 4) starting from the appropriate oxabicyclic compounds **5** and **6** and using an IEM/DA reaction sequence. Note that, at least in two cases, compounds showing the *cis*-fused 2,6-dioxabicyclo[4.3.0]-nonane system have been synthesized by metathesis reac-

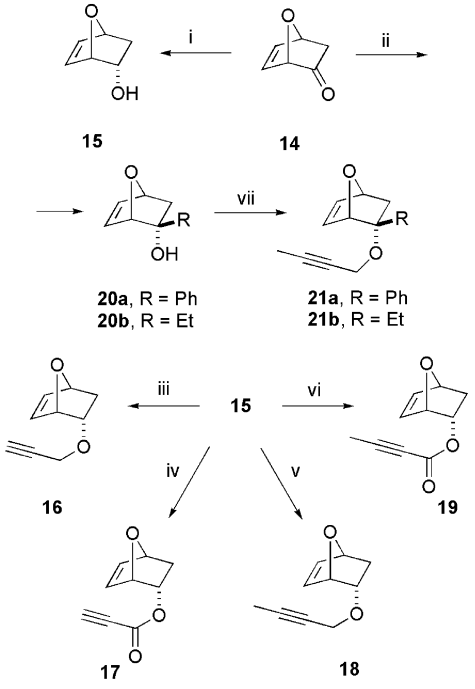
 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

tions[20] and that a part of this report has been published in a preliminary account.[21]

## Results and Discussion

### Synthesis of the General Structures 5 and 6 as Starting Materials

Racemic compounds have been used in this research. It should be noted that precursor 7-oxanorbornenone **14** (Scheme 5) has previously been obtained in optically pure form[22] and thus compounds **16**–**21** could also be synthesized in optically pure form.



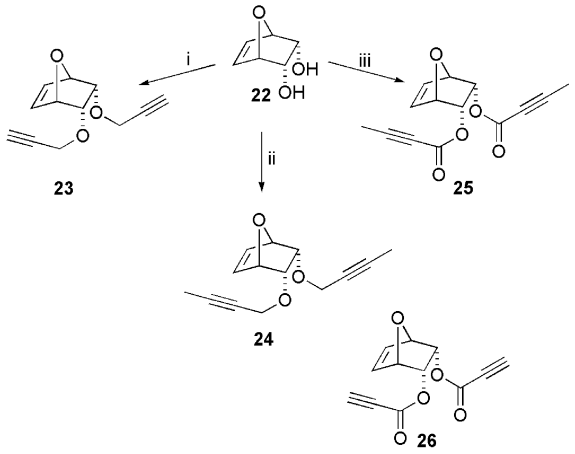

**Reagents and conditions**

i) Ref. [23]; ii) ref. [24]; iii) 3-bromopropyne (80% toluene), NaH, DMF, overnight, r.t., 94%; iv) propiolyl choride (freshly prepared from propiolic acid and oxalyl chloride), $CH_2Cl_2$, DMPA, overnight, r.t., 71%; v) 1-bromobut-2-yne, NaH, DMF, overnight, r.t., 86% or 24 h. (80%); vi) but-2-ynoic acid, $CH_2Cl_2$, DCC, $Et_3N$, DMPA, overnight, r.t., 75%; vii) 1-bromobut-2-yne, NaH, DMF, 24 h., r.t., **21a** (83%); **21b** (55%).

Scheme 5. Synthesis of 2-propargyl derivatives of 7-oxanorbornene.

Monosubstituted derivatives of the type **5** (Scheme 4) were prepared by reduction of **14**[23] ($NaBH_4$, MeOH, 90% compound **15**) or by addition of the corresponding organolithium or Grignard reagent[24] (compound **20a**, 90% with PhLi, ratio *endo*/*exo* 3.6:1, 80% with PhMgBr, only the *endo* alcohol; compound **20b**, 75% with EtMgI, only the *endo* alcohol) followed by etherification or esterification of the alcohols with the appropriate propargyl derivative. The experimental conditions and yields are summarized in Scheme 5.

Disubstituted derivatives of type **6** (Scheme 4) were synthesized from diol **22** by reaction with the appropriate propargyl derivative. The experimental conditions and yields are summarized in Scheme 6. Unfortunately all efforts to prepare compound **26** were unsuccessful under a variety of experimental conditions. Extensive decomposition of the reaction mixture was observed even at low temperatures (–5 to 0 °C) when the acid chloride or carboxylic acid were used under the experimental conditions indicated in Scheme 5 and Scheme 6.



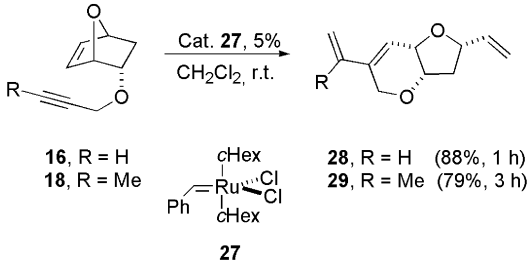

**Reagents and conditions**

i) 3-Bromopropyne (80% in toluene), NaH, DMF, orvernight, r.t., 91%; ii) 1-Bromobut-2-yne, NaH, DMF, overnight, r.t., 89%; iii) But-2-ynoic acid, $CH_2Cl_2$ , $Et_3N$, DCC, DMPA, overnight, r.t., 72%.

Scheme 6. Synthesis of the propioloyl derivatives of 7-oxanorbornene.

### Metathesis Reactions

First we explored the IEM reactions of compounds **16** and **18** by using first-generation Grubb's ruthenium catalyst **27** in the absence of an ethylene atmosphere (Scheme 7). The reactions worked well and bicyclic derivatives **28** and **29** were obtained in 88 and 79% yields, respectively.[25]

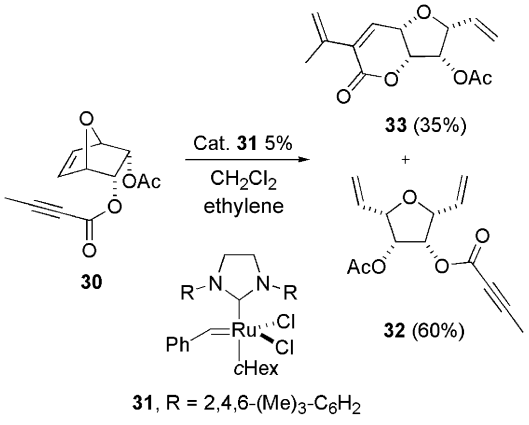



Scheme 7. Intramolecular enyne metathesis reactions of propargyl ethers **16** and **18**.

On the basis of these results, two comments appear to be opportune at this point. First, the reactions were satisfactorily achieved with both terminal and internal alkynes. Secondly, the reactions were conducted in the absence of an ethylene atmosphere. Regarding the first point, this result is noteworthy because, in general, alkyne metathesis reactions are often limited to internal acetylenic compounds,[26] al-

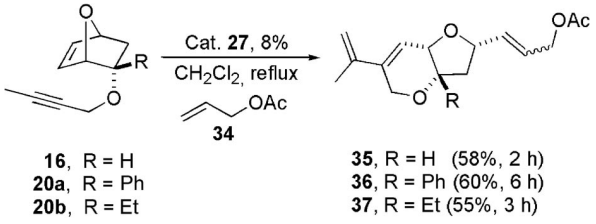
 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

though some solutions to this problem have been reported: the use of an appropriate catalyst[27] or the selection of suitable experimental conditions.[28] Nevertheless, note also that IEM reactions involving terminal alkynes have previously been observed in the norbornene series.[14] Secondly, although the beneficial effect of ethylene in IEM reactions has previously been reported,[29] we have verified[30] that the reaction of enyne **30** with catalyst **31** (5%, $CH_2Cl_2$, 24 h, ethylene) afforded tetrahydrofuran **32** as the major product (60%) together with only 35% of compound **33** arising from IEM reaction (Scheme 8).




Scheme 8. Metathesis reaction of 3-methylpropiolate **30**.

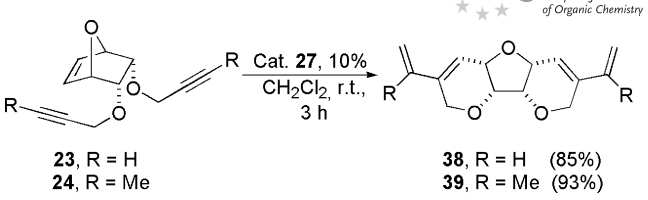
*cis*-Fused 2,6-dioxabicyclo[4.3.0]non-8-enes with alkenyl side-chains at C-3 and C-8 and also a quaternary stereogenic centre at C-5 was synthesized in the presence of catalyst **27** and 1.0 equiv. of allyl acetate **34** starting from the compounds **16** and **20a**,**b** (Scheme 9).[21] In this way the bicyclic derivatives **35**–**37** were prepared in 58, 60 and 55% yields, respectively. All these compounds were obtained as 1:1 mixtures of the *E* and *Z* isomers.




Scheme 9. Metathesis reactions of the propargyl ethers **16** and **20a**,**b** in the presence of allyl acetate **34**.

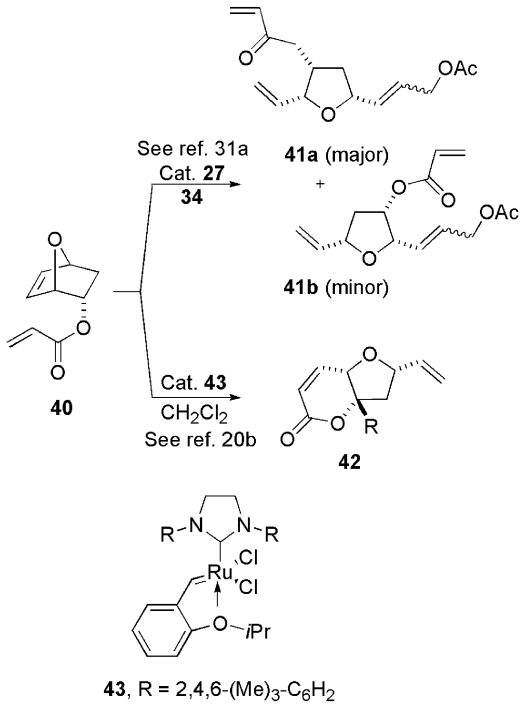
Finally, the tricyclic bis-dienes **38** and **39** were synthesized in a similar fashion starting from compounds **23** and **24**, respectively, by using catalyst **27** in the absence of ethylene (Scheme 10).

Having successfully completed the IEM reactions of the propargyl ethers we turned our attention to related esters. In these cases some previous considerations should be noted. First, the ROM/CM/RCM sequence performed on acrylates such as **40** in the presence of catalyst **27** resulted in the formation of tetrahydrofurans **41**. No traces of the bicyclic compound **42** were observed (Scheme 11).[31] Nevertheless compound **42** was prepared by using the second-




Scheme 10. Intramolecular enyne metathesis reactions of the 2,3-bis-propargyl ethers **23** and **24**.

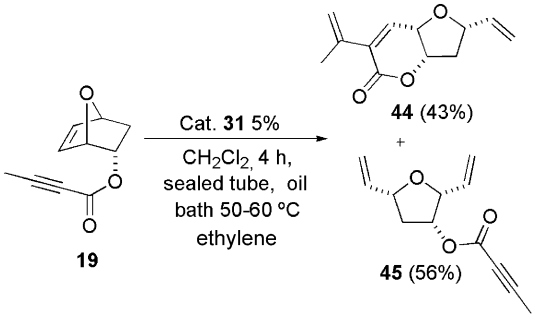
generation Hoveyda–Grubbs catalyst **43**.[32] On the other hand, catalyst **31** (Scheme 8) has proven to be very active in the presence of conjugated electron-deficient olefins[33] allowing CM reactions between α,β-unsaturated carbonyl compounds and terminal olefins. For these reasons we decided to use catalyst **31** in the IEM reactions of our 3-methylpropiolates.




Scheme 11. Metathesis reaction of acrylate **40**.

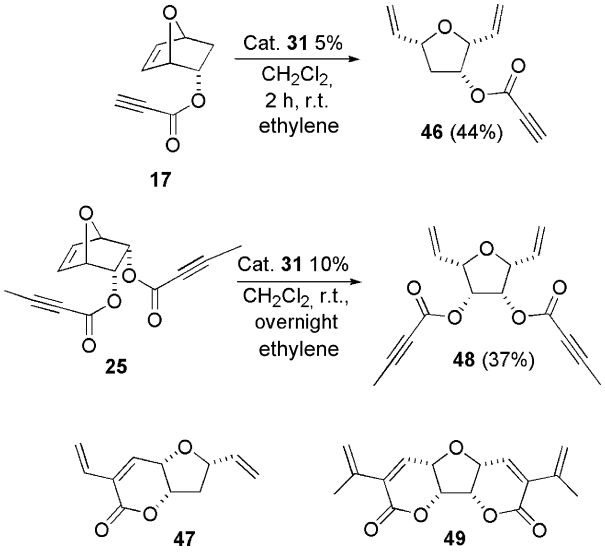
The results were satisfactory in the case of ester **19**. Treatment of this compound with catalyst **31** (10%, $CH_2Cl_2$, ethylene) gave 93% of bicycle **44** when the reaction was carried out for 75 min. The reaction time appeared to be critical in this process. For instance, after a reaction time of 90 min, compounds **45** (59%) and **44** (38%) were isolated and after 12 h the product distribution was 33% compound **45** and 50% compound **44**. On the other hand, when the reaction was conducted in $CH_2Cl_2$ (sealed tube, oil bath, 50–60 °C) a mixture containing 56% of tetrahydrofuran **45** and 43% of bicycle **44** was isolated. The ratio **45**/**44** remained essentially unchanged by the application of longer reaction times (Scheme 12).

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 




Scheme 12. Metathesis reaction of 3-methylpropiolate **19**.

In sharp contrast, compounds **17** and **25** gave disappointing results. In the case of **17** only tetrahydrofuran **46** (44% yield) was obtained with 5% catalyst **31** in $CH_2Cl_2$ (2 h, best result). Longer reaction times or the use of catalyst **43** did not improve this result. Compound **47** was never isolated although total consumption of the starting material was observed in the presence of **43** (5%, 1 h), resulting in a complex reaction mixture. Similar results were observed for compound **25**. Thus, reaction of **25** with 10% catalyst **31** gave, under ethylene, 37% of the tetrasubstituted tetrahydrofuran **48** (best conditions). Also in this case compound **49** was neither isolated nor observed under different reaction conditions (Scheme 13).

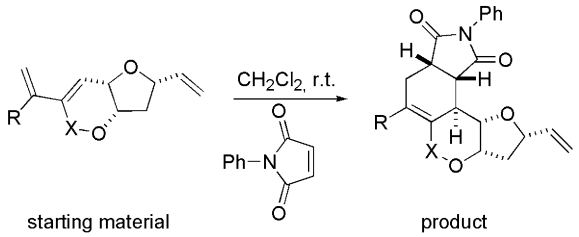



Scheme 13. Metathesis reactions of enynes **17** and **25**.

## Diels–Alder Reactions

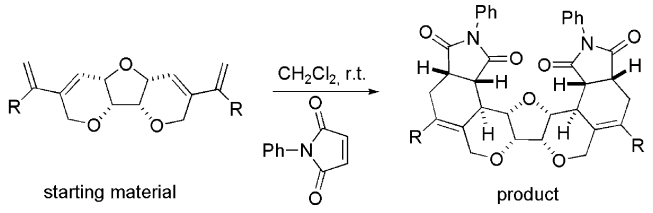
Having synthesized the dienes **28**, **29**, **38**, **39** and **42** these compounds were subjected to the Diels–Alder reaction using *N*-phenylmaleimide as the dienophilic partner. In all cases the reactions were performed in $CH_2Cl_2$ and gave the expected tetra- (**50**–**52**) or heptacyclic (**53**, **54**) derivatives in convenient yields and as a single stereoisomer (see Tables 1 and 2).

Table 1. Diels–Alder reaction of compounds **28**, **29** and **42** with *N*-phenylmaleimide. Reactions times and yields of isolated products **50**–**52**.




| Starting material X | R | | Reaction time [d] | Product | Yield [%] |
|---|---|---|---|---|---|
| $CH_2$ | H | **28** | 7 | **50** | 86 |
| $CH_2$ | $CH_3$ | **29** | 5 | **51** | 81 |
| CO | $CH_3$ | **42** | 4 | **52** | 68 |

Table 2. Diels–Alder reaction of compounds **38** and **39** with *N*-phenylmaleimide. Reactions times and yields of isolated products **53** and **54**.




| Starting material | | Reaction time [d] | Product | Yield [%] |
|---|---|---|---|---|
| R = H | **38** | 4 | **53** | 90 |
| R = $CH_3$ | **39** | 4 | **54** | 85 |

The stereochemistries of the cycloadducts **50**–**54** were established as outlined below. In the case of the tetracyclic derivatives **50**–**52**, the experimental and calculated coupling constants $^3J(H_{10b}–H_{10c})$ (AMBER method implemented in the HyperChem 7.5 package, MNDO-optimized geometries) were compared. For structure **I** (Figure 2), the calculated $^3J(H_{10b}–H_{10c})$ values lie between 0.41–0.72 Hz, whereas for structure **II** the values were estimated to be between 4.8–6.6 Hz. By comparison with the experimental values (values between 1.63–1.93 Hz, Table 3), structure **I** can be proposed as the most probable structure of the tetracyclic cycloadducts **50**–**52**.

Structure **I** was further confirmed on consideration of the long-range coupling constants (NOESY experiments) observed for compound **50** (**I**, X = $CH_2$, R = H) as a model. Correlations $H_{10a}–H_{10c}$ and $H_{10c}–H_2$ are, in this case, particularly significant and support structure **I**.

Structure **III** (Figure 2) was proposed as the structure of the heptacyclic systems **53** and **54** on the basis of the symmetrical character of these compounds, as deduced from their $^1H$ NMR spectra. NOESY experiments carried out on compound **54** (R = $CH_3$) confirmed the proposed stereochemistry. The correlations for $H_{1a}–H_{1c}$, $H_{1b}–H_{5'}$ and $H_{4a}–H_{1a}$ clearly support **III** as the structure of this compound.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

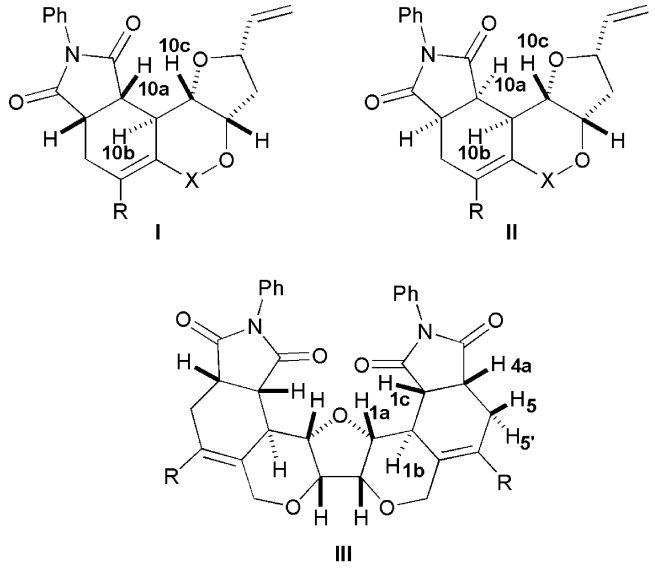



Figure 2. Proposed structures of the Diels–Alder cycloadducts **50**–**54**.

Table 3. Comparison of calculated and experimental values of $^3J(H_{10b}\text{-}H_{10c})$ for compounds **50**–**52**.

| | Calcd. $^3J(H_{10b}–H_{10c})$ for **I** [Hz] | Calcd. $^3J(H_{10b}–H_{10c})$ for **II** [Hz] | Exp. $^3J$ [Hz] |
|---|---|---|---|
| **50** | 0.41 | 5.8–6.5 | 1.60 |
| **51** | 0.60–0.70 | 6.6 | 1.80 |
| **52** | 0.56–0.72 | 4.8 | 1.90 |

## Conclusions

In this paper the IEM/DA reaction sequence has been optimized for a series of propargyl derivatives with the 7-oxabicyclo[2.2.1]hept-5-ene skeleton. In the IEM reaction, bi- or tricyclic compounds bearing a *cis*-fused 2,6-dioxabicyclo[4.3.0]nonane subunit with three or four well-defined stereogenic centres were synthesized. In addition, by selection of the appropriate starting materials, a quaternary stereogenic centre may also be created. These compounds bear dienic or bis-dienic substructures prone to Diels–Alder reaction with the appropriate dienophilic agent. In this way tetra- and heptacyclic derivatives of the *cis*-fused 2,6-dioxabicyclo[4.3.0]nonane skeleton with five and nine stereogenic centres, respectively, were also synthesized. The sequence described herein is an atom-economic entry to these kinds of compounds.

## Experimental Section

**General Information:** All reactions were carried out under argon using standard techniques. All solvents were reagent grade. Dichloromethane was freshly distilled from calcium hydride. DMF was used after distillation. All other reagents and solvents were used as supplied. Flash chromatography was performed with silica gel 60 (230–400 mesh). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. $^1$H and $^{13}$C NMR spectra were recorded with Bruker AM-200 (200 MHz) and AM-300 (300 MHz) NMR spectrometers in deuteriochloroform or deuteriated benzene. The proton ($^1$H NMR) and carbon ($^{13}$C NMR) signals were assigned on the basis of DEPT 135, COSY 45, HMQC and HMBC experiments. Chemical shifts are expressed as $\delta$ values in ppm and coupling constants are given in Hz. Melting points were determined by using a Gallenkamp instrument and are uncorrected. IR spectra were obtained with a Perkin–Elmer 781 apparatus in $CHCl_3$ solution. Elemental analyses were carried out by using a Perkin–Elmer 2400 CHN apparatus at the Complutense University, Madrid.

**Starting Materials:** Compounds **15**,[23] **20a**,**b**[24] and **22**[20b] have been described previously.

**General Procedure for the Synthesis of Compounds 16 and 18:** NaH (1.2 mmol) and the corresponding bromoalkyne (1.2 mmol) were added to a solution of compound **15** (1.0 mmol) in anhydrous DMF (6 mL/mmol) under argon at 0 °C. The reaction mixture was stirred at room temp. for 24 h. After the reaction was complete, the reaction mixture was treated with 1 N HCl (10 mL) and then extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with 5% $NaHCO_3$ (3 × 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified as indicated in each case.

**Compound 16:** NaH (28.3 mg, 1.2 mmol) and 3-bromopropyne (0.14 mL, 1.2 mmol) were added to a solution of **15** (120.0 mg, 1.07 mmol) in DMF (6.5 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) gave 151.0 mg (94%) of pure **16** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.54 (dd, $J$ = 10.83, 4.00 Hz, 1 H, 2-H), 6.35 (dd, $J$ = 5.90, 1.60 Hz, 1 H, 3-H), 5.06 (dd, $J$ = 4.10, 1.40 Hz, 1 H, 4-H), 4.94 (dd, $J$ = 4.80, 1.60 Hz, 1 H, 1-H), 4.31 (ddd, $J$ = 7.90, 4.40, 2.50 Hz, 1 H, 5-H), 4.14 (ddd, $J$ = 16.00, 12.10, 2.40 Hz, 1 H, HC≡CC$H_2$O), 2.48 (t, $J$ = 2.40 Hz, 1 H, $H$C≡CCH$_2$O), 2.22 (ddd, $J$ = 12.00, 8.00, 4.90 Hz, 1 H, 6-H), 1.11 (dd, $J$ = 11.70, 2.40 Hz, 1 H, 6′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 137.38 (C-2), 132.36 (C-3), 79.98 (HC≡$C$CH$_2$O), 79.36 (C-1), 78.40 (C-4), 76.65 (C-5), 74.86 (H$C$≡CCH$_2$O), 57.77 (HC≡C$C$H$_2$O), 33.21 (C-6) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3282, 3004, 2950, 2857, 2115, 1091, 1024 cm$^{-1}$. $C_9H_{10}O_2$ (150.07): calcd. C 71.98, H 6.71; found C 72.13, H 6.86.

**Compound 18:** NaH (24.0 mg, 0.98 mmol) and 1-bromobut-2-yne (0.11 mL, 0.98 mmol) were added to a solution of **15** (100.0 mg, 0.89 mmol) in DMF (5.4 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) gave 126.0 mg (86%) of pure **18** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.52 (dd, $J$ = 5.90, 1.70 Hz, 1 H, 2-H), 6.33 (dd, $J$ = 5.90, 1.70 Hz, 1 H, 3-H), 5.03 (dm, $J$ = 4.20 Hz, 1 H, 4-H), 4.94 (dm, $J$ = 4.70 Hz, 1 H, 1-H), 4.27 (ddd, $J$ = 7.90, 4.30, 2.50 Hz, 1 H, 5-H), 4.07 (dquint., $J$ = 10.60, 2.30 Hz, 2 H, CH$_3$C≡CC$H_2$O), 2.19 (ddd, $J$ = 11.70, 7.90, 5.0 Hz, 1 H, 6-H), 1.85 (t, $J$ = 2.30 Hz, 3 H, C$H_3$C≡CCH$_2$O), 1.09 (dd, $J$ = 11.70, 2.30 Hz, 1 H, 6′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 137.60 (C-2), 132.61 (C-3), 83.21 (CH$_3$C≡$C$CH$_2$O), 79.64 (C-1), 78.77 (C-4), 76.77 (C-5), 75.55 (CH$_3$$C$≡CCH$_2$O), 58.53 (CH$_3$C≡C$C$H$_2$O) 33.42 (C-6), 4.05 ($C$H$_3$C≡CCH$_2$O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3392, 2952, 2243, 1713, 1259, 1156, 1082, 1026 cm$^{-1}$. $C_{10}H_{12}O_2$ (164.08): calcd. C 73.15, H 7.37; found C 73.29, H 7.48.

**General Procedure for the Synthesis of Compounds 21a and 21b:** NaH (1.9 mmol) and 1-bromobut-2-yne (2.5 mmol) were added to a solution of the starting material **20a** and **20b** (1.0 mmol) in anhydrous DMF (6 mL/mmol) under argon at 0 °C. Then the reaction mixture was stirred at room temp. for 24 h. After the reaction was complete, the reaction mixture was hydrolysed with $H_2O$ (3 mL) and then extracted with $Et_2O$ (3 × 4 mL). The combined organic

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

layers were washed with $H_2O$, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified as indicated in each case.

**Compound 21a:** NaH (36.0 mg, 0.76 mmol) and 1-bromobut-2-yne (0.09 mL, 1.0 mmol) were added to a solution of **20a** (75.0 mg, 0.4 mmol) in DMF (2.0 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 2:1) gave 80.0 mg (83%) of pure **21a** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.25–7.60 (m, 5 H, Ar), 6.65 (dd, $J$ = 4.9, 1.5 Hz, 2 H, 2-H, 3-H), 5.15 (d, $J$ = 1.4 Hz, 1 H, 4-H), 4.95 (dd, $J$ = 5.6, 1.5 Hz, 1 H, 1-H), 4.00 (d, $J$ = 12.0 Hz, 1 H, $CH_3C{\equiv}CCH_2O$), 3.95 (d, $J$ = 12.0 Hz, 1 H, $CH_3C{\equiv}CCH_2O$), 2.25 (dd, $J$ = 11.8, 4.9 Hz, 1 H, 6-H), 1.85 (s, 3 H, $CH_3C{\equiv}CCH_2O$), 1.80 (d, $J$ = 11.8 Hz, 1 H, 6′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 142.1, 138.1, 134.2, 128.6, 127.2, 126.7 (C-Ar), 85.1 (C-5), 83.5 (C-4), 81.4 ($CH_3C{\equiv}\mathit{C}CH_2O$), 79.3 (C-1), 74.2 ($CH_3\mathit{C}{\equiv}CCH_2O$), 54.1 ($CH_3C{\equiv}C\mathit{C}H_2O$), 42.5 (C-6), 3.7 ($\mathit{C}H_3C{\equiv}CCH_2O$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2220, 1660, 1215 cm$^{-1}$. $C_{16}H_{16}O_2$ (240.12): calcd. C 79.97, H 6.71; found C 80.15, H 6.92.

**Compound 21b:** NaH (63.0 mg, 1.3 mmol) and 1-bromobut-2-yne (0.11 mL, 1.8 mmol) were added under argon to a solution of **20b** (100.0 mg, 0.71 mmol) in DMF (4.3 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 3:1) gave 75.0 mg (55%) of pure **21b** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.45 (dd, $J$ = 4.9, 1.5 Hz, 2 H, 2-H, 3-H), 4.85 (dd, $J$ = 5.6, 1.5 Hz, 1 H, 1-H), 4.55 (d, $J$ = 1.4 Hz, 1 H, 4-H), 3.80 (m, 2 H, $CH_3C{\equiv}CC\mathit{H}_2O$), 1.95 (dd, $J$ = 11.2, 5.9 Hz, 1 H, 6-H), 1.80 (m, 5 H, $C\mathit{H}_3C{\equiv}CCH_2O$, $CH_3C\mathit{H}_2$), 1.40 (d, $J$ = 11.2 Hz, 1 H, 6′-H), 0.90 (t, $J$ = 7.2 Hz, 3 H, $C\mathit{H}_3CH_2$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 136.5 (C-2 or C-3), 134.1 (C-2 or C-3), 82.1 (C-5), 80.9 (C-4), 80.4 ($CH_3C{\equiv}\mathit{C}CH_2O$), 79.3 (C-1), 74.2 ($CH_3\mathit{C}{\equiv}CCH_2O$), 52.6 ($CH_3C{\equiv}C\mathit{C}H_2O$), 38.6 (C-6), 28.1 ($\mathit{C}H_2CH_3$), 9.5 ($CH_2\mathit{C}H_3$), 3.7 ($\mathit{C}H_3C{\equiv}CCH_2O$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2225, 1650, 1225 cm$^{-1}$. $C_{12}H_{16}O_2$ (192.12): calcd. C 74.97, H 8.39; found C 75.05, H 8.54.

**Esterification Reactions of Compound 15. Synthesis of 3-Methylpropiolates 17 and 19**

**Compound 17:** Propiolyl chloride (120 mg, 1.35 mmol, freshly prepared from the corresponding acid) and DMPA (5.4 mg, 0.05 mmol) were added to a solution of compound **15** (50.0 mg, 0.45 mmol) in $CH_2Cl_2$ (2.2 mL) under argon at 0°°C. The reaction mixture was stirred at room temp. overnight. After this time 1 N HCl was added (7 mL) and the mixture was then extracted with $CH_2Cl_2$ (3 × 10 mL). The crude reaction was washed with $NaHCO_3$ (saturated solution, 15 mL) and NaCl (saturated solution, 15 mL) and the organic layer dried with $MgSO_4$. After filtration the solvent was removed in vacuo and the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 52.0 mg (71%) of pure **17** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.60 (dd, $J$ = 5.90, 1.80 Hz, 1 H, 5-H), 6.32 (dd, $J$ = 5.90, 1.40 Hz, 1 H, 6-H), 5.21 (ddd, $J$ = 8.00, 4.40, 2.30 Hz, 1 H, 2-H), 5.15 (dm, $J$ = 4.30 Hz, 1 H, 1-H), 5.01 (dd, $J$ = 4.70, 1.40 Hz, 1 H, 4-H), 2.89 (s, 1 H, $\mathit{H}C{\equiv}CCH_2O$), 2.38 (ddd, $J$ = 13.20, 7.90, 4.70 Hz, 1 H, 3-H), 1.23 (dd, $J$ = 12.30, 2.00 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 152.85 ($HC{\equiv}C\text{-}\mathit{C}O_2$), 138.63 (C-5), 132.05 (C-6), 79.54 (C-4), 78.00 (C-1), 75.59 ($H\mathit{C}{\equiv}C\text{-}CO_2$), 74.76 ($HC{\equiv}\mathit{C}\text{-}CO_2$), 73.03 (C-2), 33.33 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3258, 2922, 2851, 2115, 1713, 1233, 1025 cm$^{-1}$. $C_9H_8O_3$ (164.16): calcd. C 65.85, H 4.91; found C 65.94, H 5.13.

**Compound 19:** $Et_3N$ (0.28 mL, 2.0 mmol), but-2-ynoic acid (84.0 mg, 2.0 mmol), DMPA (16.0 mg, 0.13 mmol) and DCC (414.0 mg, 2.0 mmol) were added to a solution of compound **15** (150.0 mg, 1.30 mmol) in $CH_2Cl_2$ (7.0 mL, 5 mL/mmol) under argon at 0 °C. The reaction mixture was stirred under argon at room temp. overnight. After this time 1 N HCl was added (15 mL) and then the mixture was extracted with $CH_2Cl_2$ (3 × 12 mL). The reaction mixture was washed with $NaHCO_3$ (saturated solution, 20 mL), and NaCl (saturated solution, 20 mL) and the organic layer dried with $MgSO_4$. After filtration the solvent was removed in vacuo and the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 179.0 mg (75%) of pure **19** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.59 (dd, $J$ = 5.90, 1.80 Hz, 1 H, 5-H), 6.31 (dd, $J$ = 5.98, 1.40 Hz, 1 H, 6-H), 5.17 (ddd, $J$ = 12.10, 4.36, 2.30 Hz, 1 H, 2-H), 5.14 (m, 1 H, 1-H), 4.98 (dd, $J$ = 4.80, 1.70 Hz, 1 H, 4-H), 2.36 (ddd, $J$ = 12.10, 7.60, 4.80 Hz, 1 H, 3-H), 1.98 (s, 3 H, $C\mathit{H}_3C{\equiv}C\text{-}CO_2$), 1.22 (dd, $J$ = 12.10, 2.10 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 153.93 ($CH_3C{\equiv}C\text{-}\mathit{C}O_2$), 138.45 (C-5), 132.13 (C-6), 86.62 ($CH_3\mathit{C}{\equiv}C\text{-}CO$), 79.49 (C-4), 78.07 (C-1), 77.59 ($CH_3C{\equiv}\mathit{C}\text{-}CO$), 72.44 (C-2), 33.28 (C-3), 4.23 ($C\mathit{H}_3C{\equiv}C\text{-}CO$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3009, 2957, 2920, 2326, 2243, 1707, 1179, 1027 cm$^{-1}$. $C_{10}H_{10}O_3$ (178.06): calcd. C 67.41, H 5.66; found C 67.53, H 5.79.

**General Procedure for the Synthesis of Compounds 23 and 24:** NaH (3.0 mmol) and the corresponding bromoalkyne (3.0 mmol) were added to a solution of compound **22** (1.0 mmol) in anhydrous DMF (6 mL/mmol) under argon at 0 °C. Then the reaction mixture was stirred at room temp. for 24 h. After the reaction was complete, the reaction mixture was treated with 1 N HCl (10 mL) and then extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with 5% $NaHCO_3$ (3 × 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified as indicated in each case.

**Compound 23:** NaH (164.0 mg, 3.60 mmol) and 3-bromopropyne (0.32 mL, 3.60 mmol) were added to a solution of diol **22** (150.0 mg, 1.20 mmol) in DMF (7.0 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) gave 217.0 mg (91%) of pure **23** as a colourless oil. $^1$H NMR ($C_6D_6$, 300 MHz): $\delta$ = 6.27 (t, $J$ = 0.90 Hz, 2 H, 2-H, 3-H), 4.76 (m, $J$ = 5.90, 1.60 Hz, 2 H, 5-H, 6-H), 3.92 (dd, $J$ = 2.80, 1.50 Hz, 2 H, 1-H, 4-H), 3.79 (qd, $J$ = 16.00, 2.40 Hz, 4 H, 2 × $HC{\equiv}CC\mathit{H}_2O$), 1.92 (t, $J$ = 2.40 Hz, 2 H, 2 × $\mathit{H}C{\equiv}CCH_2O$) ppm. $^{13}$C NMR ($C_6D_6$, 75 MHz): $\delta$ = 134.85 (C-2, C-3), 80.48 (2 × $H\mathit{C}{\equiv}CCH_2O$), 79.72 (C-5, C-6), 75.33 (C-1, C-4), 74.66 (2 × $HC{\equiv}\mathit{C}CH_2O$), 57.51 (2 × $HC{\equiv}C\mathit{C}H_2O$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3287, 2961, 2925, 2115, 1126, 1113, 1093, 798 cm$^{-1}$. $C_{12}H_{12}O_3$ (204.08): calcd. C 70.57, H 5.92; found C 70.78, H 6.05.

**Compound 24:** NaH (66.0 mg, 1.40 mmol) and 1-bromobut-2-yne (0.13 mL, 1.40 mmol) were added to a solution of diol **22** (60.0 mg, 0.5 mmol) in DMF (3.0 mL) at 0 °C. Purification by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) gave 97.0 mg (89%) of pure **24** as a colourless oil. $^1$H NMR ($C_6D_6$, 300 MHz): $\delta$ = 6.36 (t, $J$ = 0.90 Hz, 2 H, 2-H, 3-H), 4.88 (m, 2 H, 5-H, 6-H), 4.13 (dd, $J$ = 2.80, 1.60 Hz, 2 H, 1-H, 4-H), 4.02 (dq, $J$ = 15.50, 2.30 Hz, 4 H, 2 × $CH_3C{\equiv}CC\mathit{H}_2O$), 1.43 (t, $J$ = 2.30 Hz, 6 H, 2 × $C\mathit{H}_3C{\equiv}CCH_2O$) ppm. $^{13}$C NMR ($C_6D_6$, 75 MHz): $\delta$ = 134.90 (C-2, C-3), 82.32 (2 × $CH_3\mathit{C}{\equiv}CCH_2O$), 79.98 (C-5, C-6), 76.38 (2 × $CH_3C{\equiv}\mathit{C}CH_2\mathit{O}$), 75.42 (C-1, C-4), 58.19 (2 × $CH_3C{\equiv}C\mathit{C}H_2O$), 3.22 (2 × $\mathit{C}H_3C{\equiv}CCH_2O$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2921, 2854, 2239, 1716, 1167, 1138, 1023 cm$^{-1}$. $C_{14}H_{16}O_3$ (232.11): calcd. C 72.39, H 6.94; found C 72.16, H 6.75.

**Esterification Reaction of 22. Synthesis of Compound 25:** But-2-ynoic acid (157.0 mg, 1.9 mmol), DMPA (38.0 mg, 0.3 mmol) and DCC (385.0 mg, 1.90 mmol) were added to a solution of compound **22** (80.0 mg, 0.62 mmol) in $CH_2Cl_2$ (3.1 mL, 5 mL/mmol) under argon at 0 °C. The reaction mixture was stirred at room temp. overnight. After this time 1 N HCl (10 mL) was added and

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

then the mixture was extracted with $CH_2Cl_2$ ($3 \times 10$ mL). The crude reaction was washed with $NaHCO_3$ (saturated solution; 15 mL), NaCl (saturated solution; 15 mL) and the organic layer dried with $MgSO_4$. After filtration, the solvent was removed in vacuo, the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) to give 117.0 mg (72%) of pure **25** as white solid (m.p. 142.7–144.6 °C). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.55 (t, $J$ = 1.00 Hz, 2 H, 5-H, 6-H), 5.22 (dd, $J$ = 2.90, 1.50 Hz, 2 H, 2-H, 3-H), 5.12 (m, 2 H, 1-H, 4-H), 1.99 (s, 6 H, C$H_3$-C≡CCO$_2$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 153.03 ($2 \times CH_3C$≡C-*C*O$_2$), 135.41 (C-5, C-6), 87.66 ($2 \times CH_3C$≡C-CO$_2$), 79.05 (C-1, C-4), 72.04 ($2 \times CH_3C$≡*C*-CO$_2$), 69.79 (C-2, C-3), 4.41 ($2 \times CH_3C$≡C-CO$_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2928, 2855, 2239, 1714, 1262, 1241, 736 cm$^{-1}$. $C_{14}H_{12}O_5$ (260.07): calcd. C 64.61, H 4.65; found C 64.40, H 4.51.

**General Procedure for the Metathesis Reactions of Compounds 16 and 18:** Catalyst **27** (0.05 mmol) in $CH_2Cl_2$ (55 mL/mmol catalyst) was added to a solution of compounds **16** and **18** (1.0 mmol) in $CH_2Cl_2$ (22 mL/mmol) under argon. This mixture was stirred at room temp. When the reaction was complete, the solvent was removed in vacuo and the reaction crude was purified as indicated in each case.

**Compound 28:** From **16** (35.0 mg, 0.23 mmol) in $CH_2Cl_2$ (5.1 mL) and **27** (9.6 mg, $12 \times 10^{-3}$ mmol) in $CH_2Cl_2$ (1.7 mL). After 1 h, the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) to give 37.0 mg (88%) **28** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.33 (dd, $J$ = 18.20, 11.00 Hz, 1 H, C-6-C*H*=CH$_2$), 5.99 (ddd, $J$ = 17.15, 10.30, 7.40 Hz, 1 H, C-2-C*H*=CH$_2$), 5.98 (m, 1 H, 7-H), 5.25 (ddd, $J$ = 17.10, 1.47, 1.40 Hz,1 H, C-2-CH=C$H_{2trans}$), 5.16–5.11 (m, 3 H, C-2-CH=C$H_{2cis}$, C-6-CH=C$H_2$), 4.47 (d, $J$ = 15.50 Hz, 1 H, 5-H), 4.34 (qm, $J$ = 7.30 Hz, 1 H, 2-H), 4.17–4.05 (m, 2 H, 5′-H, 3a-H), 3.97 (m, 1 H, 7a-H), 2.53 (ddd, $J$ = 14.10, 8.00, 6.70 Hz, 1 H, 3-H), 1.85 (ddd, $J$ = 14.10, 7.30, 1.80 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 140.02 (C-6), 139.03 (C-2-*C*H=CH$_2$), 135.82 (C-6-*C*H=CH$_2$), 122.53 (C-7), 117.00 (C-2-CH=*C*H$_2$), 114.66 (C-6-*C*H=CH$_2$), 80.40 (C-2), 76.00 (C-3a), 74.44 (C-7a), 64.55 (C-5), 40.01 (C-3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3084, 2881, 2836, 1190, 1155, 1054 cm$^{-1}$. $C_{11}H_{14}O_2$ (178.23): calcd. C 74.13, H 7.92; found C 73.91, H 8.06.

**Compound 29:** From **18** (29.0 mg, 0.18 mmol) in $CH_2Cl_2$ (4.0 mL) and **27** (7.5 mg, $9 \times 10^{-3}$ mmol) in $CH_2Cl_2$ (1.0 mL). After 3 h, the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 26.0 mg (79%) of **29** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.07 (d, $J$ = 4.50 Hz, 1 H, 7-H), 5.98 (ddd, $J$ = 17.00, 10.30, 7.40 Hz, 1 H, C-2-C*H*=CH$_2$), 5.25 (ddd, $J$ = 17.20, 1.50, 1.00 Hz, 1 H, CH=C$H_{2trans}$), 5.12 (ddd, $J$ = 10.20, 1.50, 0.80 Hz, 1 H, CH=C$H_{2cis}$), 4.99 (m, 1 H, C=C$H_2$), 4.90 (m, 1 H, C=C$H_2$), 4.50 (d, $J$ = 15.30 Hz, 1 H, 5-H), 4.33 (q, $J$ = 7.40 Hz, 1 H, 2-H), 4.13 (dt, $J$ = 15.30, 1.90 Hz, 1 H, 5′-H), 4.04 (ddd, $J$ = 6.60, 3.50, 1.80 Hz, 1 H, 3a-H), 3.96 (m, 1 H, 7a-H), 2.52 (ddd, $J$ = 14.00, 7.90, 6.60 Hz, 1 H, 3-H), 1.92 (dd, $J$ = 1.20, 0.50 Hz, 3 H, C$H_3$-C=), 1.83 (ddd, $J$ = 14.00, 7.20, 1.80 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 140.08 ($CH_3$-*C*=), 140.03 (C-6), 139.01 (*C*H=CH$_2$), 118.85 (C-7), 117.06 (CH=*C*H$_2$), 113.03 (C=*C*H$_2$), 80.39 (C-2), 76.61 (C-3a), 74.53 (C-7a), 65.58 (C-5), 40.04 (C-3), 20.54 (*C*H$_3$-C=) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 3081, 2969, 2927, 1170, 1116, 1058, 990 cm$^{-1}$. $C_{12}H_{16}O_2$ (192.12): calcd. C 74.97, H 8.39; found C 75.19, H 8.58.

**General Procedure for the Metathesis Reactions of Compounds 16, 20a and 20b in the Presence of Allyl Acetate 34:** Catalyst **27** (0.1 mmol) in $CH_2Cl_2$ (50 mL/mmol of cat.) was added to a solution of compounds **16**, **20a** and **20b** (1.0 mmol) and allyl acetate **34** (1.0 mmol) in $CH_2Cl_2$ (25 mL/mmol) under argon. This mixture was stirred at reflux and when the reaction was complete (between 2–6 h) the solvent was removed in vacuo and the reaction crude was purified as indicated in each case.

**Compound 35:** From **16** (60.0 mg, 0.36 mmol) and **34** (0.039 mL, 0.36 mmol) in $CH_2Cl_2$ (9.0 mL) and **27** (30.0 mg, 0.036 mmol) in $CH_2Cl_2$ (1.8 mL). After 2 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 3:1) to give 54.0 mg (58%) of **35** as a mixture (*E*/*Z* = 1:1). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.02 (d, $J$ = 4.3 Hz, 1 H, 7-H), 5.95 (m, 2 H, C*H*=C*H*), 4.98 (s, 1 H, C=C$H_2$), 4.90 (s, 1 H, C=C$H_2$), 4.75–4.40 (m, 5 H, C$H_2$OAc, 2-H, 3a-H, 7a-H), 4.15 (d, $J$ = 15.2 Hz, 1 H, 5-H), 4.02 (d, $J$ = 15.2 Hz, 1 H, 5′-H), 2.55 (m, 2 H, 3-H, 3′-H), 2.01 (s, 3 H, C$H_3$CO$_2$), 1.90 (s, 3 H, C-C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ = 172.2 ($CO_2CH_3$), 140.7 (C-6), 135.2, 126.4, 118.3 (C-7), 112.7 (C=*C*H$_2$), 78.7 (C-7a), 76.2 (C-2), 74.3 (C-3a), 65.2 ($CH_2$-O), 60.2 (C-5), 40.3 (C-3), 21.0 (C*C*H$_3$), 20.5 (*C*H$_3$CO$_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1720, 1650, 1215 cm$^{-1}$. $C_{15}H_{20}O_4$ (264.14): calcd. C 68.16, H 7.63; found C 68.32, H 7.95.

**Compound 36:** From **20a** (50.0 mg, 0.21 mmol), **34** (0.023 mL, 0.21 mmol) in $CH_2Cl_2$ (5.2 mL) and **27** (17.0 mg, 0.021 mmol) in $CH_2Cl_2$ (1.1 mL). After 6 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 4:1) to give 42.0 mg (60%) of **36** as a mixture (*E*/*Z* = 1:1). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.25–7.60 (m, 5 H, Ar), 6.15 (d, $J$ = 5.1 Hz, 1 H, 7-H), 5.75 (m, 2 H, C*H*=C*H*), 4.90 (s, 1 H, C=C$H_2$), 4.80 (s, 1 H, C=C$H_2$), 4.75–4.60 (m, 4 H, C$H_2$OAc, 2-H, 7a-H), 4.40 (d, $J$ = 16.2 Hz, 1 H, 5′-H), 3.90 (d, $J$ = 16.2 Hz, 1 H, 5-H), 2.40–2.30 (m, 2 H, 3-H, 3′-H), 2.05 (s, 3 H, C$H_3$CO), 1.95 (s, 3 H, CC$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ = 172.2 (O*C*OCH$_3$), 141.2, 140.7 (C-6), 135.2, 128.6, 127.1, 126.4, 126.1, 120.3 (C-7), 114.7 (C=*C*H$_2$), 82.3 (C-3a), 79.7 (C-7a), 77.2 (C-2), 66.2 ($CH_2$-O), 62.2 (C-5), 41.4 (C-3), 21.3 (C*C*H$_3$), 20.6 (*C*H$_3$CO$_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1710, 1640, 1225 cm$^{-1}$. $C_{21}H_{24}O_4$ (340.17): calcd. C 74.09, H 7.11; found C 74.30, H 7.24.

**Compound 37:** From **20b** (40.0 mg, 0.33 mmol), **34** (0.036 mL, 0.33 mmol) in $CH_2Cl_2$ (8.2 mL) and **27** (27.0 mg. 0.033 mmol) in $CH_2Cl_2$ (1.7 mL). After 3 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 3:1) to give 32.0 mg (55%) of **37** as a mixture (*E*/*Z* = 1:1). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 5.95 (d, $J$ = 4.9 Hz, 1 H, 7-H), 5.65 (m, 2 H, C*H*=C*H*), 5.00 (s, 1 H, C=C$H_2$), 4.90 (s, 1 H, C=C$H_2$), 4.75–4.60 (m, 4 H, C$H_2$OAc, 2-H, 7a-H), 4.40 (d, $J$ = 16.8 Hz, 1 H, 5-H), 4.10 (d, $J$ = 16.8 Hz, 1 H, 5′-H), 2.20 (m, 2 H, 3-H, 3′-H), 2.05 (s, 3 H, C$H_3$CO), 1.95 (s, 3 H, CC$H_3$), 1.35 (q, $J$ = 7.0 Hz, 2 H, $CH_3$C$H_2$), 0.95 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$) ppm. $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ = 172.8 ($CO_2CH_3$), 140.7 (C-6), 135.2, 126.4, 117.3 (C-7), 110.6 (C=*C*H$_2$), 79.8 (C-3a), 77.6 (C-7a), 73.2 (C-2), 69.2 ($CH_2$-O), 60.4 (C-5), 39.8 (C-3), 25.2, 21.0 (C*C*H$_3$), 20.5 (*C*H$_3$CO$_2$), 9.1 (*C*H$_3$CH$_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1715, 1650, 1220 cm$^{-1}$. $C_{17}H_{24}O_4$ (292.17): calcd. C 69.84, H 8.27; found C 69.93, H 8.34.

**General Procedure for the Metathesis Reactions of Compounds 23 and 24:** Catalyst **27** (0.1 mmol) in $CH_2Cl_2$ (55 mL/mmol of catalyst) was added to a solution of compounds **23** and **24** (1.0 mmol) in $CH_2Cl_2$ (22 mL/mmol) under argon. This mixture was stirred at room temp. and when the reaction was complete, the solvent was removed in vacuo and the reaction crude was purified as indicated in each case.

**Compound 38:** From **23** (40.0 mg, 0.20 mmol) in $CH_2Cl_2$ (4.3 mL) and **27** (16.0 mg, 0.02 mmol) in $CH_2Cl_2$ (1.1 mL). After 3 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) to give 39.0 mg, (85%) of **38** as a colourless oil.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

$^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.32 (dd, $J$ = 17.90, 11.10 Hz, 2 H, 2 × C*H*=$CH_2$), 5.98 (dm, $J$ = 4.40 Hz, 2 H, 4-H, 6-H), 5.16 (br. d, $J$ = 17.90 Hz, 2 H, 2 × CH=C$H_{2cis}$), 5.14 (br. d, $J$ = 11.00 Hz, 2 H, 2 × CH=C$H_{2trans}$), 4.65 (br. d, $J$ = 15.40 Hz, 2 H, 2-H, 8-H), 4.31 (dd, $J$ = 2.80, 1.30 Hz, 2 H, 9a-H, 9b-H), 4.15 (dt, $J$ = 15.40, 2.00 Hz, 2 H, 2′-H, 8′-H), 4.02 (m, 2 H, 4a-H, 5a-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 140.15 (C-3, C-7), 135.31 (2 × *C*H=$CH_2$), 121.30 (C-4, C-6), 114.75 (2 × CH=*C*$H_2$), 76.24 (C-9a, C-9b), 73.16 (C-4a, C-5a), 64.38 (C-2, C-8) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2853, 1067, 1013, 893 cm$^{-1}$. $C_{14}H_{16}O_3$ (232.11): calcd. C 72.39, H 6.94; found C 72.22, H 6.72.

**Compound 39:** From **24** (35.0 mg, 0.15 mmol) in $CH_2Cl_2$ (3.3 mL) and **27** (12.0 mg, 0.015 mmol) in $CH_2Cl_2$ (0.8 mL). After 3 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) to give 36.5 mg (93%) of **39** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.09 (br. d, $J$ = 4.10 Hz, 2 H, 4-H, 6-H), 5.02 (, 2 H, 2 × $CH_3$-C=C$H_2$), 4.94 (br. s, 2 H, 2 × $CH_3$-C=C$H_2$), 4.69 (br. d, $J$ = 15.10 Hz, 2 H, 2-H, 8-H), 4.30 (dd, $J$ = 2.80, 1.30 Hz, 2 H, 9a-H, 9b-H), 4.19 (dt, $J$ = 15.10, 2.00 Hz, 2 H, 2′-H, 8′-H), 4.05 (m, 2 H, 4a-H, 5a-H), 1.92 (s, 6 H, 2 × C*H*$_3$-C=$CH_2$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 141.65 (2 × $CH_3$-*C*=$CH_2$), 140.22 (C-3, C-7), 117.98 (C-4, C-6), 113.37 (2 × $CH_3$-C=*C*$H_2$), 76.21 (C-9a, C-9b), 73.62 (C-4a, C-5a), 65.68 (C-2, C-8), 20.48 (2 × *C*$H_3$-C=$CH_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2853, 1722, 1121, 1055, 1016, 889 cm$^{-1}$. $C_{16}H_{20}O_3$ (260.33): calcd. C 73.82, H 7.74; found C 74.06, H 7.50.

**General Procedure for the Metathesis Reactions of Compounds 17 and 19:** Catalyst **31** (0.05 mmol) in $CH_2Cl_2$ (55 mL/mmol of cat.) was added to a solution of compounds **17** and **19** (1.0 mmol) in $CH_2Cl_2$ (22 mL/mmol) under argon. This mixture was stirred at different temperatures. When the reaction was complete, the solvent was removed in vacuo and the reaction crude was purified as indicated in each case.

**Compounds 44 and 45:** From **19** (20.0 mg, 0.14 mmol) in $CH_2Cl_2$ (2.5 mL) and **31** (4.0 mg, 0.006 mmol) in $CH_2Cl_2$ (0.3 mL). After 4 h ($CH_2Cl_2$, sealed tube, oil bath 50–60 °C) the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 8:2) to give 10.0 mg (43%) of **44** and 13.0 mg (56%) of **45** both as colourless oils.

**Compound 44:** $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 6.75 (d, $J$ = 5.60 Hz, 1 H, 7-H), 5.92 (ddd, $J$ = 17.20, 10.15, 7.15 Hz, 1 H, C*H*=$CH_2$), 5.46 (m, 1 H, C$H_2$=C), 5.28 (dt, $J$ = 17.20, 1.20 Hz, 1 H, CH=C$H_{2trans}$), 5.21 (q, $J$ = 1.55 Hz, 1 H, C$H_2$=C), 5.17 (dt, $J$ = 10.15, 1.20 Hz, 1 H, CH=C$H_{2cis}$), 5.00 (ddd, $J$ = 6.20, 4.20, 2.30 Hz, 1 H, 3a-H), 4.48 (q, $J$ = 7.15 Hz, 1 H, 2-H), 4.29 (dd, $J$ = 5.60, 4.20 Hz, 1 H, 7a-H), 4.48 (q, $J$ = 7.15 Hz, 1 H, 2-H), 2.62 (ddd, $J$ = 14.20, 8.30, 6.20 Hz, 1 H, 3-H), 2.20 (ddd, $J$ = 14.20, 6.20, 2.30 Hz, 1 H, 3′-H), 2.00 (dd, $J$ = 1.30, 0.8 Hz, 3 H, C$H_3$C=) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 161.13 (C-5), 139.37 (C-6), 137.70 (*C*H=$CH_2$), 136.40 ($CH_2$=*C*), 133.73 (C-7), 118.99 (*C*$H_2$=C), 117.39 (CH=*C*$H_2$), 79.98 (C-3a), 79.81 (C-2), 71.08 (C-7a), 39.89 (C-3), 22.00 (*C*$H_3$C=) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2922, 2857, 17204, 1246, 1070, 1057 cm$^{-1}$. $C_{12}H_{14}O_3$ (206.09): calcd. C 69.88, H 6.84; found C 69.63, H 6.96.

**Compound 45:** $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 5.95 (ddd, $J$ = 17.30, 10.20, 7.20 Hz, 1 H, C-5-C*H*=$CH_2$), 5.90 (ddd, $J$ = 17.10, 10.40, 6.60 Hz, 1 H, C-2-C*H*=$CH_2$), 5.46–5.36 (m, 2 H, C-2-CH=C$H_2$, 3-H), 5.33–5.25 (m, 2 H, 2 × CH=C$H_2$), 5.17 (dt, $J$ = 10.20, 1.20 Hz, 1 H, C-5-CH=C$H_2$), 4.41–4.32 (m, 2 H, 2-H, 5-H), 2.57 (ddd, $J$ = 14.00, 7.70, 6.60 Hz, 1 H, 4-H), 1.99 (s, 3 H, C$H_3$C≡$CCO_2$), 1.88 (ddd, $J$ = 14.00, 7.20, 3.40 Hz, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 153.51 ($CH_3$C≡C*C*$O_2$), 138.50 (C-5-*C*H=$CH_2$), 132.72 (C-2-*C*H=$CH_2$), 119.59 (C-2-CH=*C*$H_2$), 117.23 (C-5-CH=*C*$H_2$), 86.66 ($CH_3$*C*≡$CCO_2$), 82.80 (C-2), 79.21 (C-5), 77.27 (C-3), 72.62 ($CH_3$C≡*C*$CO_2$), 39.21 (C-4), 4.31 (*C*$H_3$C≡$CCO_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3082, 2987, 2919, 2848, 2240, 1708, 1254, 1073 cm$^{-1}$. $C_{12}H_{14}O_3$ (206.09): calcd. C 69.88, H 6.84; found C 70.06, H 7.02.

**Compound 46:** From **17** (25.0 mg, 0.15 mmol) in $CH_2Cl_2$ (3.3 mL) and **31** (4.8 mg, 0.008 mmol) in $CH_2Cl_2$ (0.5 mL) at room temp. After 2 h the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 13.0 mg (44%) of **46** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 5.96 (ddd, $J$ = 17.30, 10.20, 7.00 Hz, 1 H, C-5-C*H*=$CH_2$), 5.89 (ddd, $J$ = 17.20, 10.40, 6.70 Hz, 1 H, C-2-C*H*=$CH_2$), 5.47–5.38 (m, 2 H, 3-H, C-2-CH=C$H_2$), 5.24 (dd, $J$ = 10.20, 1.30 Hz, 1 H, C-2-CH=C$H_{2cis}$), 5.23 (dd, $J$ = 17.20, 1.10 Hz, 1 H, C-5-CH=C$H_{2trans}$), 5.17 (dt, $J$ = 10.40, 1.20 Hz, 1 H, C-5-CH=C$H_{2cis}$), 4.43–4.33 (m, 2 H, 2-H, 5-H), 2.90 (s, 1 H, $CO_2$C≡C*H*), 2.59 (ddd, $J$ = 14.20, 7.80, 6.75 Hz, 1 H, 4-H), 1.90 (ddd, $J$ = 14.20, 7.10, 3.20 Hz, 1 H, 4′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 152.44 (HC≡C*C*$O_2$), 138.38 (C-5-*C*H=$CH_2$), 132.48 (C-2-*C*H=$CH_2$), 119.76 (C-2-CH=*C*$H_2$), 117.25 (C-5-CH=*C*$H_2$), 82.78 (C-2), 79.18 (C-5), 77.90 (C-3), 77.60 (H*C*≡$CCO_2$), 75.57 (HC≡*C*$CO_2$), 39.16 (C-4) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3528, 2922, 2851, 1713, 1233, 1025 cm$^{-1}$. $C_{11}H_{12}O_3$ (192.08): calcd. C 68.74, H 6.29; found C 68.99, H 6.42.

**Metathesis Reaction of Compound 25:** Catalyst **31** (8.7 mg, 0.0015 mmol) in $CH_2Cl_2$ (0.8 mL, 55 mL/mmol of catalyst) was added to a solution of **25** (30.0 mg, 0.14 mmol) in $CH_2Cl_2$ (3.0 mL, 22 mL/mmol) under argon. This mixture was stirred at room temp. overnight. After this time, the solvent was removed in vacuo and the reaction crude was purified by column chromatography ($SiO_2$, $CH_2Cl_2$/AcOEt, 7:3) to give 15 mg (37%) of **48** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 5.92 (ddd, $J$ = 17.30, 10.30, 7.30 Hz, 2 H, 2 × C*H*=$CH_2$), 5.51 (dd, $J$ = 4.10, 1.60 Hz, 2 H, 3-H, 4-H), 5.38 (dt, $J$ = 17.30, 1.00 Hz, 2 H, 2 × CH=C$H_{2trans}$), 5.31 (dt, $J$ = 10.30, 1.00 Hz, 2 H, 2 × CH=C$H_{2cis}$), 4.57 (ddm, $J$ = 7.30, 4.10 Hz, 2 H, 2-H, 5-H), 2.01 (s, 6 H, 2 × C*H*$_3$C≡$CCO_2$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 152.61 (2 × $CH_3$C≡C*C*$O_2$), 132.66 (2 × *C*H=$CH_2$), 120.24 (2 × CH=*C*$H_2$), 87.44 (2 × $CH_3$*C*≡$CCO_2$), 79.83 (C-2, C-5), 74.26 (C-3, C-4), 71.83 (2 × $CH_3$C≡*C*$CO_2$), 4.20 (2 × *C*$H_3$C≡$CCO_2$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 2852, 1718, 1262, 1244, 1056 cm$^{-1}$. $C_{16}H_{16}O_5$ (288.1): calcd. C 66.66, H 5.59; found C 66.89, H 5.31.

**General Procedure for the Diels–Alder Cycloaddition of Compounds 28, 29 and 44:** *N*-Phenylmaleimide (1.0 mmol) was added to a solution of compounds **28**, **29** and **44** (1.0 mmol) in $CH_2Cl_2$ (10 mL/mmol) under argon. This mixture was stirred at room temp. for 4–7 d. When the reaction was complete, the solvent was removed in vacuo and the reaction crude was purified as indicated in each case.

**Compound 50:** From **28** (20.0 mg, 0.11 mmol) in $CH_2Cl_2$ (1.0 mL) and *N*-phenylmaleimide (19.0 mg). After 7 d the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 34.0 mg (86%) of **50** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.42–7.34 (m, 3 H, Ar-H), 7.22–7.16 (m, 2 H, Ar-H), 5.97 (ddd, $J$ = 17.10, 10.30, 7.20 Hz, 1 H, C*H*=$CH_2$), 5.73 (m, 1 H, 6-H), 5.32 (dt, $J$ = 17.10, 1.30 Hz, 1 H, CH=C$H_{2trans}$), 5.18 (ddd, $J$ = 10.30, 1.30, 0.80 Hz, 1 H, CH=C$H_{2cis}$), 4.50 (dd, $J$ = 4.40, 1.60 Hz, 1 H, 10c-H), 4.40 (dd, $J$ = 4.40, 3.00 Hz, 1 H, 3a-H), 4.32 (dm, $J$ = 14.00 Hz, 1 H, 5-H), 4.21 (q, $J$ = 7.20 Hz, 1 H, 2-H), 3.88 (dqd, $J$ = 14.00, 2.50, 1.80 Hz, 1 H, 5′-H), 3.49 (dd, $J$ = 8.80, 5.90 Hz, 1 H, 10a-H), 3.34 (ddd, $J$ = 8.80, 7.20, 1.40 Hz, 1 H, 7a-H), 2.85 (ddd, $J$ = 15.25, 7.20, 1.40 Hz, 1 H, 7-H), 2.80 (m, 1 H, 10b-H), 2.57 (dd, $J$ = 14.00, 7.20 Hz, 1 H, 3-H), 2.27 (m, 1

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

H, 7′-H), 1.82 (ddd, $J$ = 14.00, 8.40, 3.00 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 178.91 (C-10), 178.09 (C-8), 138.34 (*C*H=$CH_2$), 136.88 (C-5a), 132.18 (C-Ar), 129.55 (2×CH-Ar), 129.10 (CH-Ar), 126.82 (2×CH-Ar), 119.76 (C-6), 117.24 (CH=*C*$H_2$), 78.44 (C-2), 78.18 (C-3a), 77.00 (C-10c), 66.27 (C-5), 44.23 (C-10a), 40.94 (C-7a), 40.23 (C-3), 37.22 (C-10b), 25.09 (C-7) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2854, 1707, 1385 cm$^{-1}$. $C_{21}H_{21}NO_4$ (351.40): calcd. C 70.78, H 6.02; found C 70.53, H 5.80.

**Compound 51:** From **29** (17.0 mg, 0.09 mmol) in $CH_2Cl_2$ (0.9 mL) and *N*-phenylmaleimide (15.0 mg). After 5 d the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 26.0 mg (81%) of **51** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.49–7.34 (m, 3 H, Ar-H), 7.18–7.13 (m, 2 H, Ar-H), 5.93 (ddd, $J$ = 17.20, 10.20, 7.20 Hz, 1 H, C*H*=$CH_2$), 5.30 (dm, $J$ = 17.20 Hz, 1 H, CH=C$H_{2trans}$), 5.17 (dm, $J$ = 10.20 Hz, 1 H, CH=C$H_{2cis}$), 4.49 (br. d, $J$ = 14.20 Hz, 1 H, 5-H), 4.47 (dd, $J$ = 4.40, 1.80 Hz, 1 H, 10c-H), 4.31 (m, 1 H, 3a-H), 4.22 (q, $J$ = 7.20 Hz, 1 H, 2-H), 3.92 (dm, $J$ = 14.20 Hz, 1 H, 5′-H), 3.44 (dd, $J$ = 8.80, 5.60 Hz, 1 H, 10a-H), 3.31 (ddd, $J$ = 8.80, 7.20, 1.50 Hz, 1 H, 7a-H), 2.78 (m, 1 H, 10b-H), 2.68 (dd, $J$ = 14.70, 1.50 Hz, 1 H, 7-H), 2.56 (dt, $J$ = 14.00, 7.20 Hz, 1 H, 3-H), 2.38 (m, 1 H, 7′-H), 1.83 (ddd, $J$ = 14.00, 7.20, 2.70 Hz, 1 H, 3′-H), 1.71 (m, 3 H, C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 178.85 (C-10), 178.35 (C-8), 138.51 (*C*H=$CH_2$), 132.19 (C-Ar), 129.62 (2×CH-Ar), 129.13 (CH-Ar), 128.21 (C-6), 127.21 (C-5a), 126.80 (2×CH-Ar), 117.22 (CH=*C*$H_2$), 78.45 (C-2), 77.61 (C-3a), 77.45 (C-10c), 63.45 (C-5), 44.77 (C-10a), 40.86 (C-7a), 40.22 (C-3), 37.63 (C-10b), 31.70 (C-7), 18.84 (*C*$H_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2920, 2851, 1707, 1384, 1190 cm$^{-1}$. $C_{22}H_{23}NO_4$ (365.42): calcd. C 72.31, H 6.34; found C 72.56, H 6.60.

**Compound 52:** From **42** (20.0 mg, 0.1 mmol) in $CH_2Cl_2$ (1.0 mL) and *N*-phenylmaleimide (15.0 mg). After 4 d the reaction crude was purified by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) to give 23.0 mg (68%) of **52** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.51–7.38 (m, 3 H, Ar-H), 7.14–7.10 (m, 2 H, Ar-H), 5.93 (ddd, $J$ = 17.00, 10.10, 7.80 Hz, 1 H, C*H*=$CH_2$), 5.23 (dm, $J$ = 17.00 Hz, 1 H, CH=C$H_{2trans}$), 5.13 (dm, $J$ = 10.10 Hz, 1 H, CH=C$H_{2cis}$), 5.03 (dd, $J$ = 4.60, 1.90 Hz, 1 H, 3a-H), 4.56 (d, $J$ = 1.90 Hz, 1 H, 10c-H), 4.50 (m, 1 H, 2-H), 3.53 (m, 2 H, 7a-H, 10a-H), 3.06 (m, 1 H, 10b-H), 3.01 (dd, $J$ = 15.00, 1.90 Hz, 1 H, 7-H), 2.56 (m, 2 H, 7′-H, 3-H), 2.45 (dd, $J$ = 2.30, 0.70 Hz, 3 H, C$H_3$), 2.19 (dd, $J$ = 14.30, 4.00 Hz, 1 H, 3′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 177.49 (C-10), 177.05 (C-8), 162.75 (C-5), 157.78 (C-6), 138.90 (*C*H=$CH_2$), 131.59 (C-Ar), 129.74 (2×CH-Ar), 129.51 (CH-Ar), 126.69 (2×CH-Ar), 117.12 (C-5a), 117.15 (CH=*C*$H_2$), 79.15 (C-3a), 78.80 (C-2), 76.91 (C-10c), 44.08 (C-7a), 40.76 (C-3), 39.46 (C-10a), 37.84 (C-10b), 35.41 (C-7), 24.00 (*C*$H_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2924, 2854, 1707, 1386, 1190 cm$^{-1}$. $C_{22}H_{21}NO_5$ (365.42): calcd. C 69.64, H 5.58; found C 69.87, H 5.79.

**General Procedure for the Diels–Alder Cycloaddition of Compounds 38 and 39:** *N*-Phenylmaleimide (2.0 mmol of) was added to a solution of compounds **38** and **39** (1.0 mmol) in $CH_2Cl_2$ (10 mL/mmol) under argon. After 4 d the reaction was completed, the solvent was removed at vacuo and the reaction crude was purified as indicated in each case.

**Compound 53:** From **38** (24.0 mg, 0.10 mmol) in $CH_2Cl_2$ (1.0 mL) and *N*-phenylmaleimide (36.0 mg). Purification by column chromatography ($SiO_2$, hexane/AcOEt, 1:1) gave 54.0 mg (90%) of **53** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.50–7.34 (m, 6 H, Ar-H), 7.2–7.16 (m, 4 H, Ar-H), 5.76 (br. s, 2 H, 6-H, 11-H), 4.68 (dd, $J$ = 3.40, 1.20 Hz, 2 H, 1a-H, 15c-H), 4.45 (m, 4 H, 7-H, 8a-H, 8b-H, 10-H), 3.95 (dm, $J$ = 13.70 Hz, 2 H, 7′-H, 10′-H), 3.53 (dd, $J$ = 8.70, 5.90 Hz, 2 H, 1c-H, 15a-H), 3.35 (dd, $J$ = 8.70, 6.80 Hz, 2 H, 4a-H, 12a-H), 2.86 (dd, $J$ = 15.30, 6.80 Hz, 2 H, 5-H, 12-H), 2.79 (m, 2 H, 1b-H, 15b-H), 2.30 (m, 2 H, 5′-H, 12′-H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 178.57 (C-4, C-13), 177.68 (C-2, C-15), 136.10 (C-6a, C-10a), 131.82 (2×C-Ar), 129.31 (4×CH-Ar), 128.90 (2×CH-Ar), 126.53 (4×CH-Ar), 119.89 (C-6, C-11), 78.15 (C-8a, C-8b), 74.05 (C-1a, C-15c), 67.81 (C-7, C-10), 43.29 (C-1c, C-15a), 40.21 (C-4a, C-12a), 37.26 (C-1c, C-11b), 24.29 (C-5, C-12) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3057, 2920, 2851, 1705, 1328, 1153 cm$^{-1}$. $C_{34}H_{30}N_2O_7$ (578.21): calcd. C 70.58, H 5.23; found C 70.73, H 5.40.

**Compound 54:** From **39** (16.0 mg, 0.06 mmol) in $CH_2Cl_2$ (0.6 mL) and *N*-phenylmaleimide (21.0 mg). Purification by column chromatography ($SiO_2$, hexane/AcOEt, 7:3) gave 32.0 mg (85%) of **54** as a colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.50–7.35 (m, 6 H, Ar-H), 7.19–7.14 (m, 4 H, Ar-H), 4.67 (m, 4 H, 1a-H, 7-H, 10-H, 15c-H), 4.43 (dd, $J$ = 3.50, 1.20 Hz, 2 H, 8a-H, 8b-H), 3.91 (br. d, $J$ = 14.00 Hz, 2 H, 7′-H, 10′-H), 3.48 (dd, $J$ = 8.70, 5.60 Hz, 2 H, 1c-H, 15a-H), 3.32 (ddd, $J$ = 8.70, 7.00, 1.50 Hz, 2 H, 4a-H, 12a-H), 2.76 (m, 2 H, 1b-H, 15b-H), 2.68 (dd, $J$ = 14.80, 1.50 Hz, 2 H, 5-H, 12-H), 2.40 (dd, $J$ = 14.80, 7.00 Hz, 2 H, 5′-H, 12′-H), 1.72 (s, 6 H, 2×C$H_3$) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 178.57 (C-4, C-13), 177.89 (C-2, C-15), 131.84 (2×C-Ar), 129.37 (4×CH-Ar), 128.91 (2×CH-Ar), 128.21 (C-6, C-11), 126.80 (C-6a, C-10a), 126.50 (4×CH-Ar), 126.50 (C-8a, C-8b), 74.23 (C-1a, C-15c), 64.74 (C-7, C-10), 43.60 (C-1c, C-15a), 40.21 (C-4a, C-12a), 37.86 (C-1b, C-11b), 31.46 (C-5, C-12), 18.85 (2×-*C*$H_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2923, 2853, 1705, 1384, 1090 cm$^{-1}$. $C_{36}H_{34}N_2O_7$ (606.24): calcd. C 71.27, H 5.65; found C 70.09, H 5.79.

**Supporting Information** (see also the footnote on the first page of this article). $^1$H and $^{13}$C NMR spectra for all compounds described in this paper and results of the NOESY experiments for compounds **50** and **54**. The results of the COSY (45), HMQC and HMBC NMR experiments on these compounds are available upon request from the senior author of this article.

## Acknowledgments

The Ministerio de Educación y Ciencia (MEC) (Spain, Projects 96-0641 and CTQ-2006-15279–03–01) is gratefully thanked for financial support. A. A. and M. C. M. thank the MEC for grants.

[1] For a general treatise, see: a) R. H. Grubbs (Ed.), *Handbook of Metathesis*, three-volume set, Wiley-VCH, Weinheim, **2003**. See, in particular, vol. 2, "Applications in Organic Synthesis". For other selected, comprehensive and recent accounts, see: b) R. H. Grubbs, T. M. Trnka, "*Ruthenium-Catalyzed Olefin Metathesis*" in *Ruthenium in Organic Synthesis* (Ed.: S. I. Murahashi), Wiley-VCH, Weinheim, **2006**, chapter 6; c) M. Mori, "Recent Progress in Metathesis Reactions" in *New Frontiers in Asymmetric Catalysis* (Eds.: M. Koinichi, M. Lautens), Wiley-VCH, Weinheim, **2007**, chapter 6, pp. 153–206; d) J. C. Mol, P. W. N. M. van Leeuwen, "Metathesis of Alkenes" in *Handbook of Heterogeneous Catalysis* (Eds.: G. Ertl, H. Knötzinger, F. Schüth, J. Weitkamp), 2nd ed., Wiley-VCH, Weinheim, **2008**, vol. 7, pp. 3240–3256.

[2] For two selected reviews, see: a) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251; b) S. Kotha, K. Lahiri, *Synlett* **2007**, 2767–2784.

[3] For recent reviews, see: a) S. T. Diver, *J. Mol. Catal. A* **2006**, *254*, 29–42; b) E. C. Hansen, D. Lee, *Acc. Chem. Res.* **2006**, *39*, 509–519; c) H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55–66; d) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121–135.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

[4] a) For the first report, see: A. Kinoshita, N. Sakakibara, M. Mori, *J. Am. Chem. Soc.* **1997**, *119*, 12388–12389; For the first review, see: b) M. Mori, *Alkene Metathesis in Organic Synthesis*, *Topics in Organometallic Chemistry*, Springer, Berlin, **1998**, vol. 1, pp. 133–154.

[5] a) S. Kotha, N. Sreenivasachary, E. Brahmachary, *Tetrahedron Lett.* **1998**, *39*, 2805–2808; b) S. Kotha, N. Sreenivasachary, E. Brahmachary, *Eur. J. Org. Chem.* **2001**, 787–792; c) S. Kotha, S. Halder, E. Brahmachary, *Tetrahedron* **2002**, *58*, 9203–9208; d) S. Kotha, K. Mandal, S. Banerjee, S. M. Robin, *Eur. J. Org. Chem.* **2007**, 1244–1255; e) S. Kotha, P. Khedkar, *Synthesis* **2008**, 2925–2928.

[6] a) R. Duboc, Ch. Henaut, M. Savignac, J. P. Genet, H. Bhatnager, *Tetrahedron Lett.* **2001**, *42*, 2461–2464; b) N. Desroy, F. Robert-Peillard, J. Toueg, R. Duboc, Ch. Henaut, M. N. Rager, M. Savignac, J. P. Genet, *Eur. J. Org. Chem.* **2004**, 4840–4849; c) N. Desroy, F. Robert-Peillard, J. Toueg, Ch. Henaut, R. Duboc, M. N. Rager, M. Savignac, J. P. Genet, *Synthesis* **2004**, 2665–2672.

[7] a) K. P. Kaliappan, V. Ravikumar, *Org. Biol. Chem.* **2005**, *3*, 848–851; b) K. P. Kaliappan, A. V. Subrahmanyan, *Org. Lett.* **2007**, *9*, 1121–1124.

[8] a) S. C. Schurer, S. Blechert, *Tetrahedron Lett.* **1999**, *40*, 1877–1880; b) S. Bentz, S. Laschat, *Synthesis* **2000**, 1766–1773; c) M. Moreno-Mañas, R. Pleixats, A. Santamaria, *Synlett* **2001**, 1784–1786; d) H. Guo, R. Madhusaw, F. W. Shen, R. S. Liu, *Tetrahedron* **2002**, *58*, 5627–5637; e) S. Imhof, S. Blechert, *Synlett* **2003**, 609–614; f) H. Y. Lee, H. Y. Kim, H. Tae, B. G. Kim, J. Lee, *Org. Lett.* **2003**, *5*, 3439–3442; g) Y. K. Yang, J. Tae, *Synlett* **2003**, 2017–2020; h) M. Rosillo, G. Domínguez, L. Casarrubios, U. Amador, J. Pérez-Castells, *J. Org. Chem.* **2004**, *69*, 2084–2093; i) S. Mix, S. Blechert, *Org. Lett.* **2005**, *7*, 2015–2018; j) K. C. Majumdar, H. Rahaman, S. Muhuri, B. Roy, *Synlett* **2006**, 466–468; k) S. K. Chattopadhyay, T. Biswas, K. Neogi, *Chem. Lett.* **2006**, *35*, 376–377; l) F. D. Boyer, I. Hanna, *Org. Lett.* **2007**, *9*, 715–718; m) L. Evanno, A. Deville, B. Bodo, B. Nay, *Tetrahedron Lett.* **2007**, *48*, 4331–4333; n) J. C. Lovely, Y. Chen, E. V. Ekamayake, *Heterocycles* **2007**, *74*, 873–894; o) R. Ben-Othman, M. Othman, S. Coste, B. Decroix, *Tetrahedron* **2008**, *64*, 559–567; p) S. Aritmitsu, B. Fernández, C. del Pozo, S. Fustero, G. B. Hammond, *J. Org. Chem.* **2008**, *73*, 2656–2661.

[9] C. S. Poulsen, R. Madsen, *J. Org. Chem.* **2002**, *67*, 4441–4449.

[10] Y. K. Yang, J. H. Choi, J. Tae, *J. Org. Chem.* **2005**, *70*, 6995–6998.

[11] G. Zheng, T. J. Dougherty, R. K. Pandey, R. K. Pandey, *Chem. Commun.* **1999**, 2469–2470.

[12] For a review, see: M. North, *Adv. Strain. Interesting Molecules* **2000**, *8*, 145–185.

[13] For a review, see: R. Madan, A. Srivastava, R. C. Anand, J. K. Varma, *Prog. Polym. Sci.* **1998**, *23*, 621–663.

[14] a) D. Banti, M. North, *Tetrahedron Lett.* **2002**, *43*, 1561–1564; b) D. Banti, M. North, *Adv. Synthesis Catal.* **2002**, *344*, 694–704; see also: c) E. Groaz, D. Banti, M. North, *Eur. J. Org. Chem.* **2007**, 3727–3745.

[15] For a review of metathesis reactions in oxa- and azanorbornene derivatives, see; a) O. Arjona, A. G. Csákÿ, J. Plumet, *Eur. J. Org. Chem.* **2003**, 611–622; see also: b) O. Arjona, A. G. Csákÿ, J. Plumet, *Synthesis* **2000**, 857–861; c) S. J. Connon, S. Blechert, *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923; d) R. Medel, J. Plumet, *Targets Heterocycl. Systems* **2004**, *8*, 162–186.

[16] A. Basso, L. Banfi, R. Riva, R. Guanti, *Tetrahedron* **2006**, *62*, 8830–8837.

[17] For reviews, see: a) M. Oikawa, M. Sasaki, *Tohoku J. Agricultural Res.* **2006**, *57*, 59–65; b) R. Sakai, G. T. Swanson, M. Sasaki, K. Shimamoto, H. Kamiya, *Central Nervous System Agent Med. Chem.* **2006**, *6*, 83–108; for recent synthetic approaches to these compounds and derivatives, see: c) M. Sasaki, N. Akiyama, K. Tsubone, M. Shoji, M. Oikawa, R. Sakai, *Tetrahedron Lett.* **2007**, *48*, 5697–5700; d) K. Takahashi, T. Matsumura, J. Ishihara, S. Hatakeyama, *Chem. Commun.* **2007**, 4158–4160; e) M. Sasaki, K. Tsubone, K. Aoki, N. Akiyama, M. Shoji, M. Oikawa, R. Sakai, K. Shimamoto, *J. Org. Chem.* **2008**, *73*, 264–273, and references cited within these papers.

[18] For reviews, see: a) M. A. Brimble, *Tetrahedron* **2000**, *56*, 1937–1992; b) J. Sperry, P. Bachu, M. A. Brimble, *Nat. Prod. Rep.* **2008**, *25*, 376–400, and references cited therein; see also: c) M. A. Brimble, *Pure Appl. Chem.* **2000**, *72*, 1635–1639; d) S. Claessens, G. Verniest, J. Jacobs, E. Van Hende, P. Habonimana, T. N. Van, L. Van Puyuelde, N. De Kimpe, *Synlett* **2007**, 829–850.

[19] For reviews, see: a) H. B. Mereyala, M. Joe, *Curr. Med. Chem.: Anti-Cancer Agents* **2001**, *1*, 293–300; b) G. Zhao, B. Wu, X. Y. Wu, Y. Z. Zhang, *Mini-Rev. Org. Chem.* **2005**, *2*, 333–353; c) A. de Fátima, L. V. Modolo, L. S. Conegero, R. A. Pilli, C. V. Ferrera, L. K. Kohn, J. E. de Carvalho, *Curr. Med. Chem.* **2006**, *13*, 3371–3384; d) M. Mondon, J. P. Gesson, *Curr. Org. Synth.* **2006**, *3*, 41–75; see also: e) S. H. Inayat-Hussein, A. B. Osman, L. B. Din, N. Taniguchi, *Toxicol. Lett.* **2002**, *131*, 153–159.

[20] a) M. S. M. Timmer, M. Verdoes, L. A. J. M. Sliedregt, B. A. van der Marel, J. H. van Boom, H. S. Overkleeft, *J. Org. Chem.* **2003**, *68*, 9406–9411; b) A. Aljarilla, M. C. Murcia, J. Plumet, *Synlett* **2006**, 831–832.

[21] O. Arjona, A. G. Csákÿ, M. C. Murcia, J. Plumet, *Tetrahedron Lett.* **2000**, *41*, 9777–9779.

[22] a) For a review, see: P. Vogel, J. Cossy, J. Plumet, O. Arjona, *Tetrahedron* **1999**, *55*, 13521–13642; for another method for the synthesis of **14** in an optically pure form, see: b) A. Forster, T. Kovac, H. Mosimann, P. Vogel, *Tetrahedron: Asymmetry* **1999**, *10*, 567–571.

[23] P. Vogel, D. Fattori, F. Gasparini, C. le Drian, *Synlett* **1990**, 173–185.

[24] O. Arjona, R. Fernández, A. Mallo, S. Pérez, J. Plumet, *J. Org. Chem.* **1989**, *54*, 4158–4164.

[25] The structures of the compounds synthesized in this paper were secured by IR and $^{1}H$ and $^{13}C$ NMR spectroscopy and combustion analysis. In some cases HMQC, HMBC, COSY 45 and MS experiments were also used; see Supporting Information.

[26] For illustrative accounts of alkyne metathesis, see: a) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307–2320; b) A. Mortreux, O. Coutellier, *J. Mol. Catalyst* **2006**, *254*, 96–104; for an interesting note on the mechanism of alkyne metathesis, see: c) U. H. F. Bunz, *Science* **2005**, *308*, 216–217.

[27] See, for instance: O. Coutellier, A. Mortreux, *Adv. Synth. Catal.* **2007**, *349*, 2259–2263, and references cited therein.

[28] a) J. A. Smulik, S. T. Diver, *Org. Lett.* **2000**, *2*, 2271–2274; b) J. A. Smulik, S. T. Diver, *J. Org. Chem.* **2000**, *65*, 1788–1792.

[29] M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.* **1998**, *63*, 6082–6083.

[30] A. Aljarilla, J. Plumet, *Synthesis* **2008**, 3516–3524.

[31] O. Arjona, A. G. Csákÿ, M. C. Murcia, J. Plumet, *J. Org. Chem.* **1999**, *64*, 9739–9741. For a discussion on the compatibility of catalyst **27** with conjugated electron-deficient alkenes, see pp. 1903–1904 of ref.[15c]. For a ROM–RCM reaction of an oxanorbornenic α,β-unsaturated ketone, see: C. L. Chandler, A. J. Phillips, *Org. Lett.* **2005**, *7*, 3493–3495.

[32] See ref.[20b]. Commercially available catalyst **43** shows efficiencies similar to catalyst **31** but with different substrate selectivity. Both catalysts promote ROM–CM reactions even in unstrained cycloalkenes. See, for instance: S. Randl, S. J. Connon, S. Blechert, *Chem. Commun.* **2001**, 1796–1797.

[33] See p. 1904 of ref.[15c], and references cited therein.

Received: September 25, 2008
Published Online: January 8, 2009

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 