The Sequence of a Stepwise Ad_E Reaction and Intramolecular Pauson-Khand Cycloaddition as an Entry into the Synthesis of Polycyclic Compounds

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Abstract: A stepwise Ad_E acylmethoxylation across the double bond of dicobalt hexacarbonyl complexes (DCHCC) of conjugated enynes was elaborated as an efficient and general route for the synthesis of DCHCC of 1,6-enynes containing a combination of five- and six-membered-ring fragments. Depending on the structure of these adducts, the latter either were subjected to 1,2-carbonyl reduction followed by an intramolecular Pauson-Khand (IMPK) cyclization or were directly utilized as substrates for this process. A list of model polycyclic systems which were assembled using this approach includes [5.5.5] angularly fused compounds, [6.5.5] and [5.5.5] linearly fused tricyclics, and linearly and angularly fused [6.5.5.5] and [5.5.5.5] tetracyclic products. A novel convergent and general method for the synthesis of various cyclic compounds is suggested on the basis of the Ad_E-IMPK tandem sequence as the key steps for the assemblage of polycyclic frameworks. This option seems to be especially promising for the tetracyclic derivatives mentioned above, as in these cases only two operationally simple steps are required to convert readily available starting blocks into the target structures related to natural polyquinanes.

Introduction

We have shown in previous studies that the Ad_E reaction across the double bond of a dicobalt hexacarbonyl complex (DCHCC) of conjugated enynes could be carried out in a stepwise manner as a real sequence of independent additions of an electrophile and a nucleophile via the formation of a stabilized carbocationoid intermediate (CCI).[1a,b] Since the nature of both the electrophile and nucleophile can be varied independently and over a broad range, this reaction is applicable as a general method of regiospecific 1,2-functionalization of conjugated enynes[1c,d] in accordance with the general equation represented in Scheme I.

The utilization of unsaturated electrophiles and/or nucleophiles as the addends in this reaction opened the entry into an easy preparation of variously substituted enynes from simple building blocks.[2a-c] Specifically, it was shown that this Ad_E route could serve as a short and flexible method for the synthesis of DCHCC of 1,6-enynes, valuable precursors for the intramolecular Pauson-Khand (IMPK) cyclization ([2 + 2 + 1] cycloaddition).[3a,b] Thus the sequence, Ad_E reaction followed by IMPK cyclization, was developed as a short and convergent protocol for the synthesis of a series of bicyclo[3.3.3]octenones[4a-d] and their 3-oxa analogs,[2b,4a] as is illustrated in Scheme II.[4a]

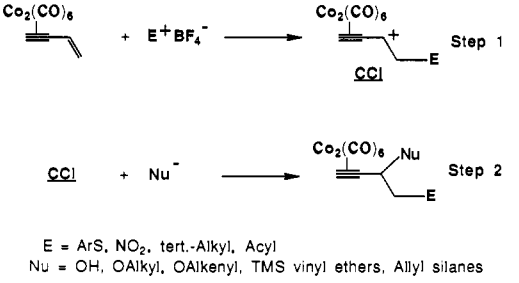
Among the options given in Scheme II, the former, based on the use of unsaturated acylium ions, was shown to be the most promising due to the ease of preparation and handling of these species belonging to various structural types.[2a,c,d]

The present study was initiated with the aim of testing the applicability of the suggested methodology to a more complicated task, namely, to the synthesis of angularly and linearly fused polycyclic systems[5] which are related to the natural polyquinanes.[6]

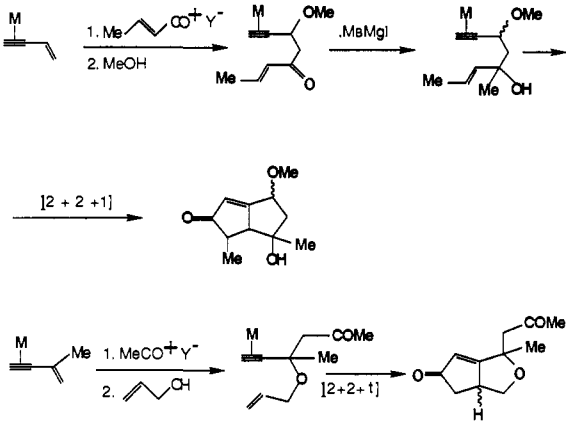
Results and Discussion

Angularly Fused Tricyclics. The synthesis of angularly fused compounds along a route similar to that outlined in Scheme II implied the use of a cyclic acyl cation as an electrophile in the Ad_E reaction. The interaction of DCHCC of vinylacetylene **1** with 1-cyclopentenoyl tetrafluoroborate **2** (the latter, as well as other acylium salts used in this study, was generated in situ via the

Scheme I



Scheme II[a]



[a] Throughout this paper M = $Co_2(CO)_6$; Y = BF_4.

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(1) (a) Schegolev, A. A.; Smit, W. A.; Kalyan, Y. B.; Krimer, M. Z.; Caple, R. *Tetrahedron Lett.* **1982**, *23*, 4419. (b) Schegolev, A. A.; Smit, W. A.; Mikaelyan, G. S.; Gybin, A. S.; Kalyan, Y. B.; Krimer, M. Z.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 2571. (c) Mikaelian, G. S.; Gybin, A. S.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1985**, *26*, 1269. (d) Mikaelyan, G. S.; Gybin, A. S.; Smit, W. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2277.

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Table I. ^{1}H NMR Data for **5a–d**[a]

	H-6	H-4	H-3	H-3	H-2	H-8	MeO	others
5a	6.16, s	4.49, dd (7.2, 5.0)	2.48, dd (15.0, 7.2)	2.28, ddd (15.0, 5.0, 4.5)	4.13, d (4.5)	2.77, d (8.5)	3.40, s	1.6–1.9, m
5b	6.06, d (1.85)	4.65, ddd (9.5, 3.1, 1.85)	2.28, ddd (17.0, 9.0, 3.1)	2.16, ddd (17.0, 9.5, 9.0)	4.22, t (9.0)	2.52, d (8.5)	3.41, s	1.6–2.1, m
5c	6.05, s	4.27, dd (7.5, 5.2)	2.49, ddd (13.5, 7.7, 7.5)	1.94, ddd (13.5, 10.0, 5.2)	3.95, dd (10.0, 7.7)	2.71, m	3.33, s	1.2–2.3, m
5d	6.17, d (1.9)	4.62, ddd (9.2, 2.4, 1.9)	2.65, ddd (15.0, 9.2, 4.7)	2.01, dd (15.0, 2.4)	4.0, d (4.7)	2.86, dd (8.5, 1.5)	3.46, s	1.4–2.0, m

[a] The ^{1}H NMR data were taken at 250 MHz in $CDCl_3$ with TMS as internal standard. *J* values are given in hertz in parentheses.

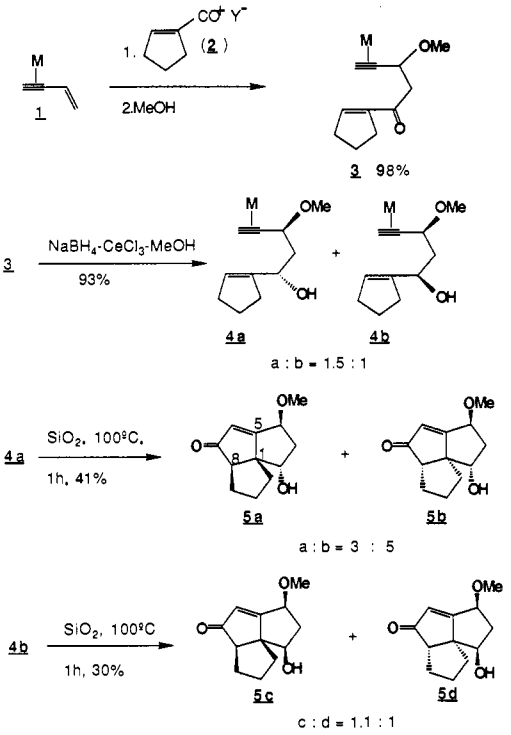
Table II. ^{13}C NMR Data for **5a–d**[a]

	C-7	C-5	C-6	C-2	C-4	C-1	C-8	C-3	C-9–11			MeO
5a	214.8	183.6	128.5	76.0	75.2	66.4	53.2	44.0	34.7	29.1	25.2	57.4
5b	213.3	183.2	126.1	76.7	73.6	64.2	57.0	40.2	29.0	27.4	23.4	57.9
5c	214.0	182.9	130.0	75.5	73.3	64.9	57.5	42.3	29.3	26.8	24.6	56.4
5d	213.6	187.8	126.8	77.9	75.6	66.5	52.9	41.6	34.8	28.6	25.2	58.0

[a] The ^{13}C NMR data were taken at 75 MHz in $CDCl_3$ with TMS as internal standard.

interaction of the respective acyl fluoride with gaseous BF_3) under the previously described conditions of methoxyacylation[2a] proceeded with an amazing efficiency and gave the expected adduct **3** in nearly quantitative yield (Scheme III). As was shown earlier,[3b,4b,c] DCHCC of 1,6-enynes bearing a carbonyl group in conjugation with the double bond, which are formed as the immediate products of Ad_E acylation of DCHCC of 1,3-enynes, are unable to undergo the IMPK reaction (see, however, data presented below in Schemes XII–XIV). Hence, additional manipulations of these adducts were required to transform the latter into suitable substrates for IMPK cyclization. Both 1,2-Grignard addition[4b] and hydride reduction[4c,d] were previously used to achieve this goal. For the adduct **3**, hydride reduction in a $NaBH_4$–$CeCl_3$–MeOH system (cf., data in ref 4d) proved to be very efficient, and the respective hydroxy product **4a,b** was obtained as a mixture of easily separable (TLC) diastereomers in excellent total yield. Attempts to perform the IMPK reaction with these substrates under conventional conditions by thermolysis in solution (liquid phase conditions, LPC, hexane, 80 °C, several hours, sealed vessel; compare with the data given in ref 3) were rather fruitless since only trace amounts of the metal-free polar compound, supposedly of the expected cycloadduct type, were detected. On the contrary, under the previously elaborated dry state adsorption conditions (DSAC[7a–c]), the cyclization of both isomers **4a** and **4b**

Scheme III



proceeded smoothly, albeit with a lower efficiency[8] than that reported for simpler models.[4a–d,7a–c]

Both reactions were nonstereospecific and led to the formation of stereoisomeric mixtures of the tricyclic products, **5a,b** and **5c,d**, respectively, (Scheme III) which were separated by TLC. The structure of adduct **5a** was shown by X-ray analysis to be (1*R**,2*S**,4*S**,8*R**)-4-methoxy-2-hydroxytricyclo[6.3.0.0^{1,5}]undec-5-en-7-one. These data also unequivocally proved the configuration of the adduct **4a** used to prepare **5a**. Since both **5a** and **5b** originate from the same isomer **4a**, these products must have the same relative anti configuration of hydroxy and methoxy groups and, hence, can differ only by the stereochemistry of the ring junction at C-1 and C-8. Products **5c** and **5d** formed from **4b** are expected to have syn-oriented MeO and HO substituents. Their structures were ascertained from the comparison of ^{1}H NMR spectral patterns of **5a–d** (Table I) and the observation of NOEs in their ^{1}H NMR spectra. In fact, a strong NOE was observed for protons at C-2 and C-11 only for **5a** and **5d**, while **5b** and **5c** exhibited an NOE between protons at C-2 and C-8.

(2) (a) Smit, W. A.; Schegolev, A. A.; Gybin, A. S.; Mikaelyan, G. S.; Caple, R. *Synthesis* **1984**, 887. (b) Smit, W. A.; Simonyan, S. O.; Mikaelyan, G. S.; Mamyan, S. S.; Gybin, A. S.; Shashkov, A. S.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 334. (c) Mikaelyan, G. S.; Smit, W. A.; Batsanov, A. S.; Struchkov, Y. T. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 2105.

(3) (a) The IMKP reaction was originally described in the following: Knudsen, M. J.; Schore, N. E. J. *J. Org. Chem.* **1984**, *49*, 5025. (b) For a general review of the reaction, see: Schore, N. E. J. The Pauson–Khand Cycloaddition Reaction for Synthesis of Cyclopentenones. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40, p 2.

(4) (a) General approach is outlined in the following: Caple, R. Utilization of Stepwise Ad_E Reactions in Designing Organic Synthesis. In *Organic Synthesis: Modern Trends*; Chizov, O., Ed.; Blackwell Scientific Publications: Oxford, UK, 1987. See also: (b) Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Struchkov, Y. T.; Kuz'mina, L. G.; Mikaelian, G. S.; Caple, R.; Swanson, E. D. *Tetrahedron Lett.* **1986**, *27*, 1241. (c) Gybin, A. S.; Smit, W. A.; Veretenov, A. L.; Simonian, S. O.; Shashkov, A. S.; Struchkov, Y. T.; Kuz'mina, L. G.; Caple, R. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2756. (d) Veretenov, A. L.; Gybin, A. S.; Smit, W. A.; Chertkov, V. A.; Shashkov, A. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 1879.

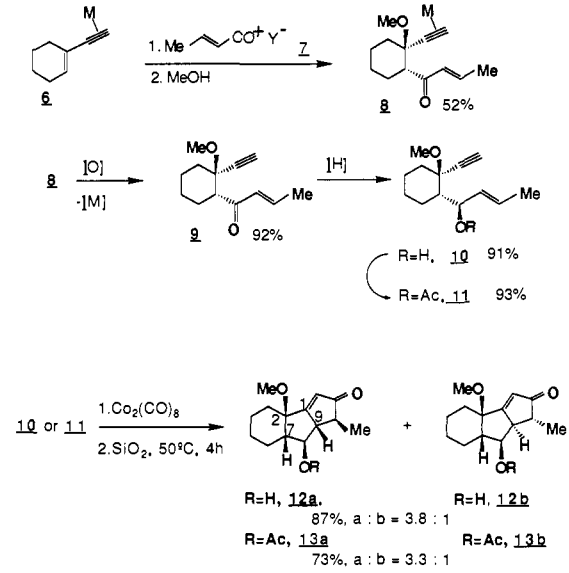
(5) For a preliminary communication, see: Smit, W. A.; Gybin, A. S.; Simonian, S. O.; Veretenov, A. L.; Shashkov, A. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1987**, 232.

(6) (a) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (b) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41.

(7) (a) Simonyan, S. O.; Smit, W. A.; Gybin, A. S.; Shashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245. (b) Smit, W. A.; Simonyan, S. O.; Tarasov, V. A.; Mikaelian, G. S.; Gybin, A. S.; Ibragimov, I. I.; Caple, R.; Froen, D. E.; Kreager, A. *Synthesis* **1989**, 472. (c) Smit, W. A.; Simonian, S. O.; Tarasov, V. A.; Shashkov, A. S.; Mamyan, S. S.; Gybin, A. S.; Ibragimov, I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1988**, 2796.

(8) No yield optimization was tried. Most low yields were usually due to noticeable (TLC) decomplexation of the initial substrates.

Scheme IV



Analysis of the spin–spin coupling of the proton at C-6 also provided useful criteria for the stereochemical assignments. In fact, previous data for a series of substituted bicyclo[3.3.0]octenones revealed that the proton at C-6 appeared as a singlet in ^{1}H NMR spectra of the diastereoisomers with an endo orientation of the proton at C-4, while a doublet with J_4 = 1.8–2.0 was observed in ^{1}H NMR spectra of isomers having an exo proton at C-4.[4c,d] A similar pattern of splitting was observed for the pairs **5a,c** (H-6, singlets) and **5b,d** (H-6, doublets) (see Table I).

The nonstereospecificity of the **4** → **5** conversion closely paralleled the observations reported earlier by Neil Shore's group concerning the steric course of the IMPK reaction which had been used for the synthesis of angularly fused triquinanes with a different pattern of substitution.[3b,9a,b] It is also worthwhile to note that the results of our previous studies on the steric course of the formation of the bicyclo[3.3.0] system from 1,6-enynes bearing substituents both at the allylic and propargylic sites[4b–d,7a–c] also attest to a rather low stereoselectivity in cycloadditions for the polysubstituted substrates in the absence of a discriminating bulky substituent.

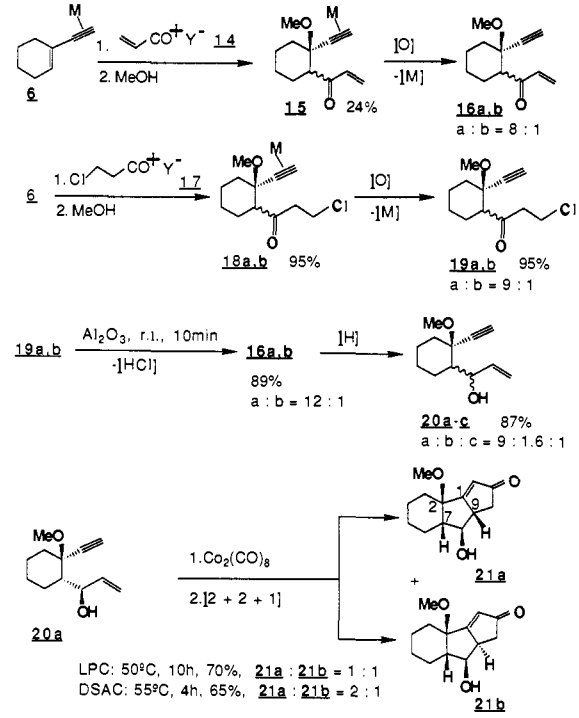
Linearly Fused Tricyclics. The suggested tandem sequence of Ad_E plus IMPK reactions can be applied to the synthesis of the title systems,[5] provided DCHCC of cycloalkenylacetylenes are used as starting materials.

We have found that this route is especially useful for the synthesis of the [6.5.5] framework from DCHCC of 1-ethynylcyclohexene **6**. Thus, methoxyacylation of the latter compound with crotonoyl tetrafluoroborate **7**[2a] proceeded readily and gave the desired trans adduct **8** with the *E* configuration of the double bond in a satisfactory yield[10] (Scheme IV).

Unfortunately, attempts to achieve direct reduction of the carbonyl group in **8** under the conditions successfully used for **3** failed. To circumvent this problem, adduct **8** was converted into the decomplexed ketone **9** (upon treatment with cerium(IV) ammonium nitrate), and the latter was smoothly reduced into the respective allyl alcohol **10** (a single stereoisomer was formed), which was further transformed into the acetate **11** (Scheme IV). Single-crystal X-ray analysis of the latter established its structure as (1*R**,2*R**,1′*R**)-1-methoxy-1-ethynyl-2-[(*E*)-1′-acetoxybut-2′-enyl]cyclohexane.

Treatment of **10** (or **11**) with $Co_2(CO)_8$ followed by the IMPK reaction under DSAC led to the formation of the tricyclic adduct, 10-methyl-8-hydroxy(or acetoxy)-2-methoxytricyclo[7.3.0.0^{2,7}]-dodec-1(12)-en-11-one **12** (or **13**) in good yield. In both cases, the conversion proceeded in a stereoselective manner, giving as major products stereoisomers **12a** or **13a**. Cyclization of **10a** under LPC proceeded with a lower efficiency as compared with DSAC; adduct **12** was formed in 39% yield after heating the substrate in hexane at 60 °C for several hours (TLC data indicated the complete conversion of the starting material).

Scheme V



The 2*R**,7*S**,8*R** configuration for diastereomers **12a,b** (or **13a,b**) follows from the configuration of the corresponding centers in the starting material **10** (or **11**). Relative configurations at C-9 and C-10 in **12a** (or **13a**), as represented in Scheme IV, were established from the observation of NOEs in ^{1}H NMR spectra of **13a** and **13b**.[11]

Acylation of **6** with acryloyl tetrafluoroborate **14** proceeded in a more complicated manner, and the yield of the desired acyl methoxy adduct **15** never exceeded 24% despite all attempts to secure better results by modifications in the reaction conditions.[12] Hence, an alternative route was devised based upon the use of 3-chloropropionyl tetrafluoroborate **17** as a masked equivalent of **14**. Reaction of **6** with **17** under standard conditions gave adducts **18a,b** as a mixture of stereoisomers in nearly quantitative yield. Oxidative decomplexation of this mixture produced **19a,b** (a:b = 9:1). The latter, when applied to the surface of Al_2O_3 (basic), underwent smooth dehydrochlorination,[13] accompanied by a partial isomerization, and yielded enones **16a,b** enriched with the major isomer **16a**. Hydride reduction of **16a,b** proceeded smoothly and gave allyl alcohol **20** as a mixture of three isomers (Scheme V). The major component, **20a** was isolated in 67% yield. Treatment of **20a** with $Co_2(CO)_8$ followed by IMKP reaction produced the tricyclic enones **21a,b** as a mixture of two isomers in a good total yield.

(9) (a) Schore, N. E.; Knudsen, M. J. *J. Org. Chem.* **1987**, *52*, 569. (b) Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224.

(10) Adduct **8** was formed as a mixture of *E* and *Z* isomer configurations of the double bond (total yield 65%, ratio 5:1). Formation of the latter isomer is obviously due to partial isomerization of the reacting acylium cation **7** since the starting acyl fluoride contains ca. 5% *Z* isomers (^{1}H NMR). Only the *E* isomer was used in further reactions. The same refers to the preparation of adduct **29** (vide infra).

(11) The stereochemistry shown was additionally ascertained from the analysis of the splitting pattern for vicinal $J_{^1H-^1H}$ and $J_{^{13}C-^1H}$ in comparison with earlier data for the series of substituted bicyclo[3.3.0]octenone derivatives.[4c,d] A detailed discussion of these data will be published separately.

(12) TLC monitoring revealed that the reaction of **6** with **14** proceeded quite cleanly. The low yields of **15** are obviously due to the increased propensity of this adduct to undergo polymerization under the conditions of its isolation and purification (cf. data in ref 4d).

(13) This dehydrochlorination procedure was elaborated earlier as the method of choice for similar adducts prepared by the acylation of acyclic enynes.[4d]

Table III. ^{1}H NMR Data for Substituted Tricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-ones (250 MHz, $CDCl_3$)[a]

	H-12	H-8	OMe	H-9	H-10n	H-10x	H-7	Me	H-3–H-6
13a	6.02	4.44	3.19	2.76	2.35		2.23	1.22	H-6n 0.85, m, 1.2–2.2, m
	d	dd	s	dddd	dq		ddd	d	
13b	5.92	5.21	3.32	2.98	2.27		2.3	1.12	1.2–2.0, m
	d	dd	s	ddd	m		m	d	
21a	6.04	3.50	3.25	3.13	2.23	2.88	2.12		H-6x, n 0.8, m, 1.1–1.9, m
	d	m	s	dddd	dd	dd	m		
21b	5.94	4.10	3.28	3.25	2.62	2.37	2.13		1.2–2.0, m
	d	dd	s	m	dd	dd	m		
27a	5.95	3.49	3.20		2.33	2.43	2.25...	1.31	H-6x 1.86, m
	s	d	s		d	d	ddd	s	H-6n 1.19, m, 1.3–1.8, m
27c	5.86	4.00	3.14		2.79	2.05	2.44	1.28	1.2–2.0, m
	s	d	s		d	d	m	s	
27d	5.81	3.88	3.20		2.28	2.57	1.53	1.31...	H-3x 2.37, dt
	s	dd	s		d	d	m	s	H-3n 1.23, m, 1.2–1.9, m
27f	5.77	3.92	3.09		2.84	2.07	1.29	1.35	H-3x 2.29, dt
	s	d	s		d	d	m	s	H-3n 1.24, m
									H-6x 1.27, m
									H-6n 1.73, m, 1.1–1.8, m

[a] In the spectra of **13a** and **13b** the protons of the Ac group appears as singlets at 2.07 and 2.04 ppm, respectively. Coupling constants (Hz): $J_{7,8}$ = 3.0 (**13a**), 7.4 (**13b**), 3.7 (**21a**), 5.4 (**21b**), 7.0 (**27a**), 5.5 (**27c**), 6.0 (**27d**), 9.0 (**27f**); $J_{8,9}$ = 5.2 (**13a**), 9.2 (**13b**), 1.6 (**21a**), 7.5 (**21b**); $J_{9,10x}$ = 7.0 (**21a**), 7.8 (**21b**); $J_{9,10n}$ = 4.2 (**13a**), 4.3 (**13b**), 4.2 (**21a**), 3.7 (**21b**); $J_{10x,10n}$ = 16.2–18.2 for all compounds; $J_{9,12}$ = 2.3–2.5 for **13a,b** and **21a,b**; $J_{7,9}$ = 1.1 (**13a**) and 0 (**13b**); $J_{8,OH}$ = 12.1 (for **27f** only!).

Table IV. ^{13}C NMR Data for **13a,b** and **27a,c,d,f** (75 MHz, $CDCl_3$, TMS)[a]

	C-11	C-1	C-12	C-8	C-2	C-9	C-7	MeO	C-10	C-3–C-6				Me
13a	210.9	181.1	127.4	80.6	77.3	57.3	52.1	50.9	50.4	28.5	28.0	23.4	22.0	14.0
13b	209.7	184.6	121.6	72.0	77.3	51.7	47.6	51.4	44.4	29.0	22.0	20.1	18.9	14.0
27a	209.3	188.1	128.1	80.9	80.5	52.4	51.7	54.6	53.1	27.2	24.6	20.4	18.9	21.5
27c	211.3	189.3	127.2	76.4	80.5	54.0	52.0	51.5	47.1	26.7	20.9	20.9	18.6	26.3
27d	209.2	192.4	124.1	77.4	82.8	52.9	53.8	52.4	56.0	27.3	25.4	21.7	20.3	24.4
27f	211.3	191.8	123.8	79.6	81.5	52.1	58.6	52.1	49.0	27.3	25.6	23.5	20.3	29.3

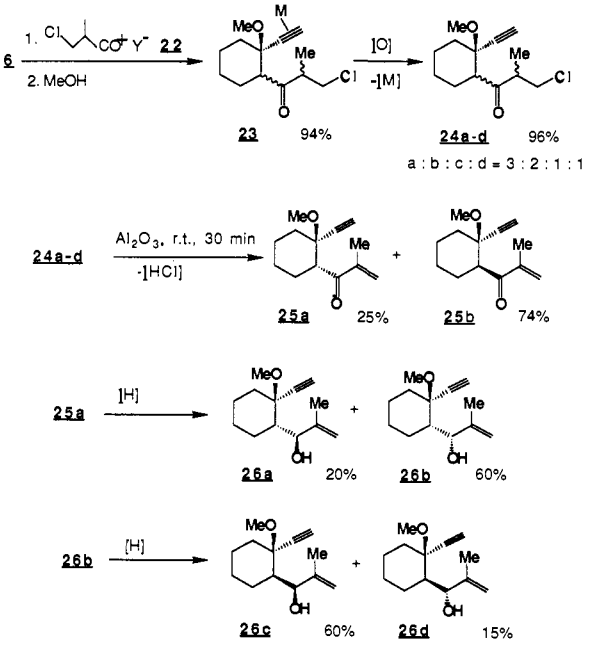
[a] Signals of the CH_3COO group present in **13a** and **13b** appear at 170.9 and 21.2 ppm (for **13a**) and 170.2 and 21.2 ppm (for **13b**).

In this case, the IMKP reaction proceeded with comparable ease both under LPC and DSAC. However, in the latter case, a slightly higher stereoselectivity was observed. Products **21a** and **21b** were separated by TLC. Their structures (and hence the stereochemistry of the precursor **20a**) were ascertained from the observation of NOEs in ^{1}H NMR spectra and by comparison of the latter with the respective data for **12a,b**[11] (Table III).

A direct acylation of **6** with methacryloyl tetrafluoroborate was also found to be unsuitable as a preparative method due to the low yield and instability of the product under the reaction conditions and/or product isolation. By analogy with the above mentioned precedent this problem was solved by the use of 2-methyl-3-chloropropionyl tetrafluoroborate **22** as an acylating agent. The corresponding adduct **23** was prepared in nearly quantitative yield (Scheme VI). Further decomplexation into **24** (mixture of four isomers in the ratio 3:2:1:1, ^{1}H NMR data) and dehydrochlorination of the latter over Al_2O_3 resulted in formation of the methacryloyl methoxy adduct **25a,b** in an excellent overall yield. It was rather surprising to find out that the sequence of reactions leading from **6** to **25** produced, predominantly, isomer **25b** with a cis orientation of the acyl and methoxy groups, while a similar sequence applied to the preparation of an acryloyl analog gave, as the major product, **16a** with a trans configuration of these groups (cf. data in Schemes V and VI). Individual products **25a** and **25b** were further reduced under standard conditions into the corresponding allyl alcohols **26a,b** and **26c,d**. In both cases, 1,2-carbonyl reduction proceeded as a stereoselective process (Scheme VI). The stereochemistry of **26a–d** as well as that of the starting ketones **25a,b** was inferred from the data on the structure of the final tricyclic products derived therefrom (vide infra).

Upon treatment with $Co_2(CO)_8$, **26a–d** were converted into the corresponding DCHCCs. IMPK cyclization of these complexes turned out to be a fairly efficient process under both LPC and DSAC. The stereochemistry varied from high selectivity (for **26a,c**) to complete specificity (for **26b,d**). It should be noted again that the cyclization of **26c** under DSAC revealed higher selectivity as compared with LPC (Scheme VII). The structure of the

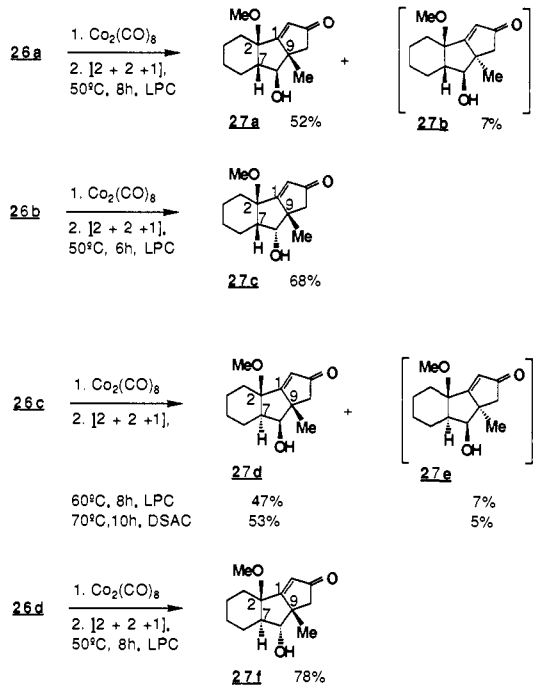
Scheme VI



tricyclic adducts as stereoisomers of 9-methyl-8-hydroxy-2-methoxytricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-ones **27a,c,d,f** (minor isomers **27b,e** have not been isolated in a pure state) was deduced from the observation of NOEs in their ^{1}H NMR spectra and by comparison of the patterns of ^{1}H and ^{13}C NMR spectra of these products with the data for the above mentioned linearly fused tricyclic products[11] (Tables III and IV).

The successful synthesis of the linearly fused [6.5.5] tricyclic system, starting from **6**, encouraged us to apply a similar sequence of transformations for 1-ethynylcyclopentene **28** with the hope of arriving at the [5.5.5] tricyclic framework common to many

Scheme VII



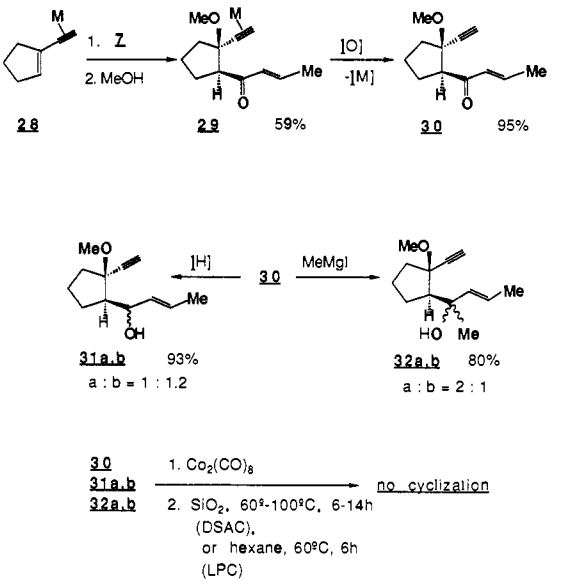
natural triquinanes.[6] One might have anticipated that in this case the stereochemical problems would be much more critical in comparison with the synthesis of the [6.5.5] system described above. In fact, it is well known that, due to the steric strain, trans fusion of five-membered rings is extremely unfavorable[6a] and hence the application of the IMPK reaction for the construction of this system requires the use of precursors having 1,2-cis-oriented ethynyl and propenyl groups.

Albeit the ease of acylmethoxylation of **28** is well documented,[2a] at the beginning of this study no reliable data were available on the steric course of this reaction. By analogy with the data on the stereochemistry of the Ad_E reactions in the cyclohexene series (see Schemes IV and V), we did not expect any special problems in securing the preparation of the necessary stereoisomers by the standard procedure of acylmethoxylation of **28**. In fact the reaction of **28** with **7** proceeded quite cleanly and gave (after quenching of the reaction mixture with MeOH at −20 °C) the corresponding adduct DCHCC **29** in a fair yield[10] (Scheme VIII). Oxidative decomplexation converted **29** into a crystalline crotonoyl methoxy adduct **30**. However, much to our dismay, an examination of its structure by X-ray single-crystal analysis revealed that the latter had the structure of (1*R**,2*S**)-1-methoxy-1-ethynyl-2-[(*E*)-1′-oxobut-2′-enyl]cyclopentane!

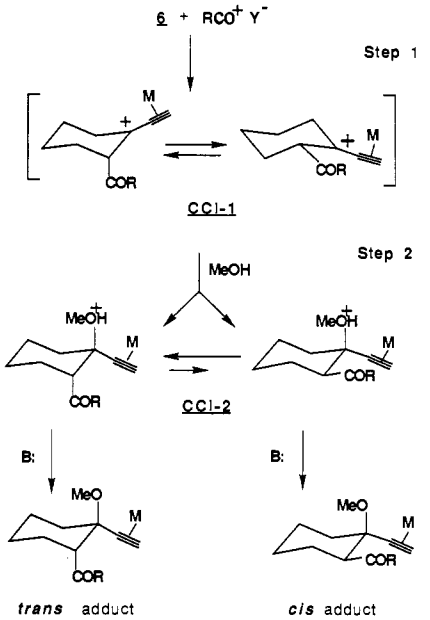
Thus the acylation of **28** also proceeded stereospecifically but as an exclusive cis addition across the double bond, in striking contrast to the aforementioned data relating to the similar reaction performed with **6**. Nevertheless, some attempts were made to check the possibility of carrying out the IMPK reaction in the cyclopentane series with a "wrong" configuration of the reacting side chains. To this aim, **30** was converted into the secondary allyl alcohols **31a,b** (by 1,2-hydride reduction) or into the tertiary allyl alcohols **32a,b** (by 1,2-addition of MeMgI at −70 °C). Not unexpectedly, DCHCC derived from both **31** and **32** failed to undergo cycloaddition under all conditions tested (LPC or DSAC), and the starting materials were either intact or turned into an untractable tar. Cyclization was also not observed with ketone **30** (Scheme VIII).

These results forced us to look more thoroughly at the problem of control over the stereochemistry of the acylmethoxylation of **28**. Earlier data on the acylation of **6**, revealed that the stereochemistry of the final adduct could vary depending on the conditions used for the quenching of the carbocationic intermediate (CCI) with a nucleophile.[2a,c] Thus the treatment of the CCI formed upon the interaction of **6** with various acylium cations with

Scheme VIII



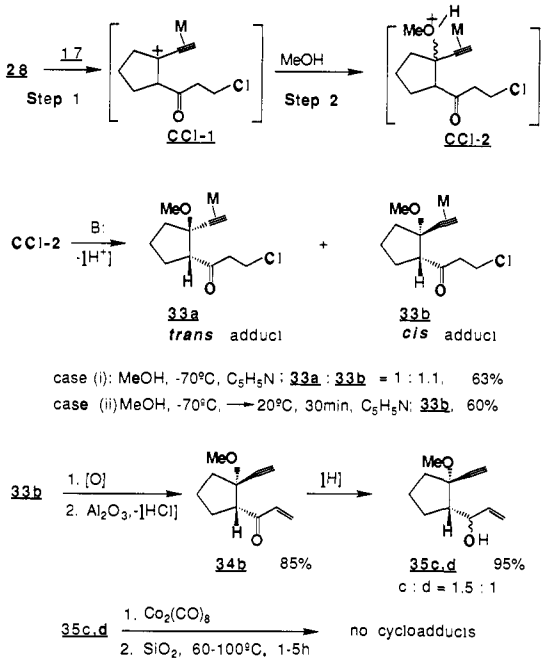
Scheme IX



MeOH at −70 °C followed by an *immediate neutralization* with a base at low temperature led to the formation of a mixture of cis and trans adducts. At the same time almost exclusive formation of the trans adduct (such as **8**, **16a**, or **18a**; see above) was observed when the reaction mixture formed upon the quenching of the CCI with MeOH was allowed to warm up to −20 °C and was kept for 1–2 h at this temperature prior to neutralization with a base (the conditions used in the reactions are shown in Schemes IV and V). Rationalization of these data was given[2c] in terms of the nonstereoselectivity of the quenching of CCI-1 under kinetic control and the possibility of further equilibration (in the absence of the base) of the initially formed mixture of stereoisomeric protonated methoxy adducts CCI-2 (via elimination–addition) into the more stable trans adduct (Scheme IX).

To check the possibility of exerting similar control in the addition across the double bond of the five-membered, ring we have studied the course of the acylmethoxylation of **28** with **17**. The reaction mixture formed upon addition of the acyl cation was quenched with MeOH at −70 °C and then either (i) neutralized immediately with pyridine at this temperature or, alternatively, (ii) warmed up to 20 °C, kept for 30 min at ambient temperature, cooled to −70 °C, and neutralized again with pyridine. In apparent corroboration of the data discussed above for the reactions with

Scheme X



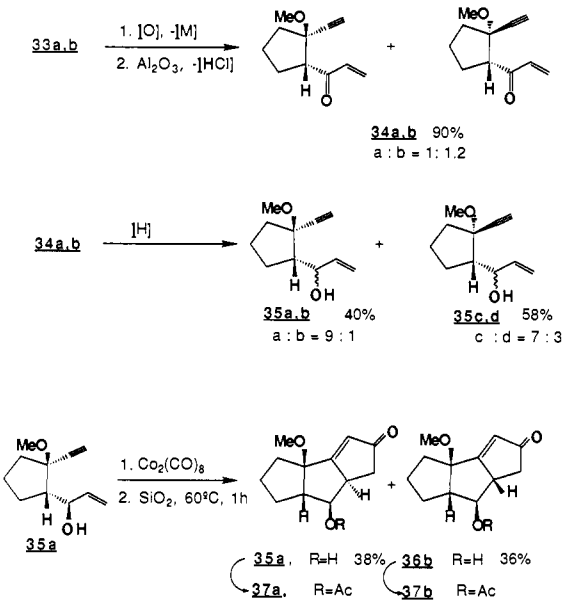
6, the kinetically formed product (case i) was comprised of a nearly 1:1 mixture of two isomers, **33a** and **33b**. As was expected under the conditions of thermodynamic control (case ii), a practically pure single isomer **33b** was formed. Unfortunately, analysis of the ^{1}H NMR spectrum of the corresponding decomplexed sample did not allow us to determine the stereochemistry of **33b**. Hence, an attempt was made to use **33b** as the starting compound for preparation of the tricyclic product. The sequence of the oxidative decomplexation and dehydrochlorination gave **34b**, which further underwent smooth 1,2-hydride reduction with the formation of allyl alcohols **35c,d** (Scheme X).

All attempts to use **35c,d** as substrates for IMKP cyclization, however, proved to be futile. These results unequivocally indicated a cis orientation of addends in **33b** in spite of the fact that the latter was prepared under conditions previously and quite successfully used for preparation of the desirable trans adduct in the cyclohexane series. It became obvious then that pursuing our goal could be achieved only with the use of isomer **33a** as a starting material. To check this option, the above mentioned mixture **33a,b** was subjected to oxidative decomplexation followed by dehydrochlorination (Scheme XI). The mixture of stereoisomers, **34a,b** thus formed was reduced to the mixture of alcohols **35a–d**. After separation by chromatography, pure isomer **35a** was isolated in 36% yield. To our delight, this product turned out to be a very suitable precursor for the IMPK reaction. In fact treatment of **35a** with $Co_2(CO)_8$ followed with heating of the resulting Co complex under DSAC gave the required product, 2-methoxy-7-hydroxytricyclo[6.3.0.0^{2,6}]undec-11-en-10-one **36a,b**, in 74% yield. It has also been found that the entire sequence **33** → **36** can be carried out without a chromatographic separation of the stereoisomeric intermediates. In this case, products **36a,b** were obtained in a yield of ca. 30%, which roughly corresponded to the percentage of the reactive isomer in the initial mixture.

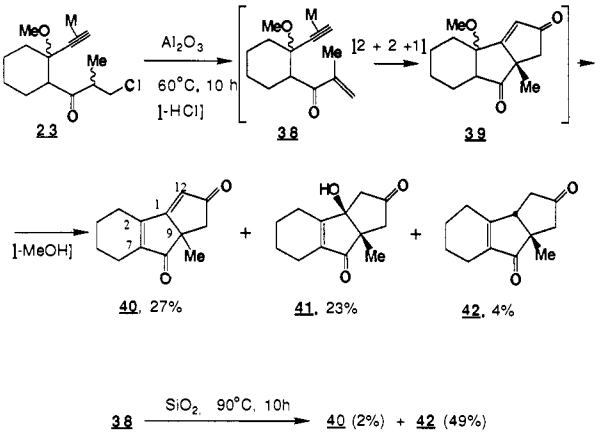
As is shown in Scheme XI, the resulting cycloadduct represents a mixture of diastereoisomers **36a** and **36b**. Acetylation of this mixture followed by TLC separation afforded individual tricyclics **37a** and **37b**. The structure of **37a** as (2*R**,6*S**,7*R**,8*R**)-7-acetoxy-2-methoxytricyclo[6.3.0.0^{2,6}]undec-11-en-10-one represented in Scheme XI was elucidated by X-ray analysis. The stereochemistry of isomer **37b** was deduced from comparison of ^{1}H NMR spectral patterns and observation of NOEs for both isomers.

IMPK Cyclizations with the Participation of a Conjugated Double Bond in the Synthesis of Polycyclic Compounds. While we were trying to optimize the procedure for the preparation of

Scheme XI



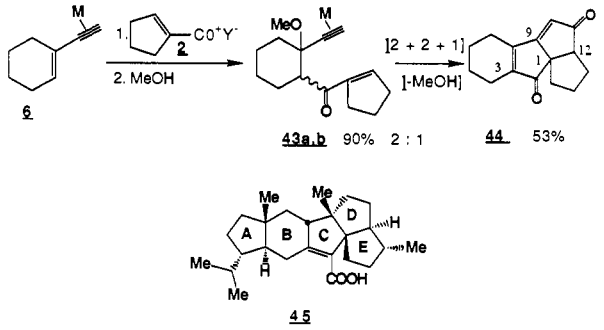
Scheme XII



25, attempts were made to carry out the dehydrochlorination of **23** over basic Al_2O_3 without prior decomplexation of **23** into **24** (Scheme VI). TLC monitoring revealed that HCl elimination with **23** proceeded easily even at room temperature, but in addition to the target product **38** (DCHCC of **25**; Scheme XII), metal-free and more polar compounds were formed in varying amounts. Under slightly more forceful conditions (60 °C), the conversion of **38** into these products was complete within 10 h. Much to our surprise (and delight) we discovered that the resulting mixture was comprised mainly of the tricyclic products **40–42** formed in a satisfactory total yield (Scheme XII). Thus, in spite of the presence of the carbonyl functionality in conjugation with the double bond, adduct **38** turned out to be amenable to the IMPK reaction under the conditions mentioned.

The structures of **40–42** were deduced from their spectra (IR, UV, HRMS, and NMR). Thus the UV spectra of **41** and **42** revealed the presence of adsorption bands with λ_{max} 235 and 237 nm, respectively, indicative of the presence of an α,β-disubstituted cyclopentenone moiety. For **40**, two band appeared with λ_{max} 117 and 292 nm, typical for the presence of an extended dienedione system. The presence of the latter is also indicated by the appearance of adsorption bands at 1596 and 1608 (conjugated double bonds) and 1706 with a shoulder at 1698 cm^{-1} (carbonyl groups) in the IR spectrum for **40**. IR spectra of **41** and **42** indicated the presence of one double bond (1658 cm^{-1}) and two carbonyl groups (1706 and 1748 cm^{-1}). The ^{1}H NMR spectrum of **40** contained a singlet at δ 5.73 (H at C-12) and an AB multiplet at δ 2.27 and 2.44. ^{1}H NMR spectra of **42** revealed an AA'BB' multiplet of four α-carbonyl protons with small long-range coupling constants

Scheme XIII



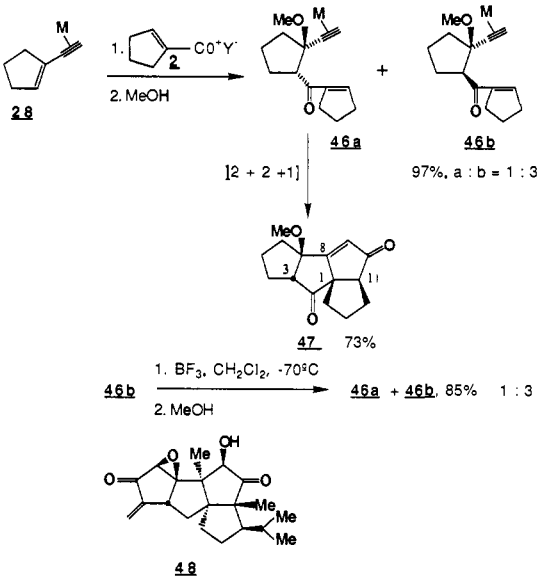
between protons at C-10 and C-12; for **41**, protons at C-12 were additionally coupled with a proton at C-1. ^{13}C NMR spectra of **40–42** indicated the presence of 13 carbon atoms having the expected pattern of chemical shifts (see the Experimental Section). The stereochemistry of **42** is substantiated by the observation of NOEs. A similar configuration for **41** is ascertained by the noticeable upfield shift of the Me signal in its ^{13}C NMR spectrum (γ-gauche effect of hydroxyl group) as compared with the respective signal for **42**.

The results shown in Scheme XII implied that under DSAC a series of consecutive reactions with **23** occurred, namely, rapid dehydrochlorination leading to **38**, IMPK cyclization of the latter accompanied by elimination of methanol giving **40**, and Michael addition of water (from Al_2O_3) across the less hindered site of **40** leading eventually to **41**. The same mixture **40–42** was also obtained by the cyclization of preformed adduct **38** over Al_2O_3. One can reasonably assume, then, that the IMPK reaction initially produces the tricyclic methoxy enone **39**. In fact, TLC data indicated the transient appearance of another polar product at the initial period of the cyclization. We were unable, however, to isolate **39** in a pure state due to the ease of its transformation into a mixture of **40** and **41** in the course of the attempted isolation by PTLC (on Fluorisil). The presence of **39** in this mixture was ascertained by MS and ^1H NMR data (appearance of the respective molecular ion M^+ 234 and signals of methoxy groups at δ 3.13 and 3.20). Formation of the product **42** indicated the occurrence of hydrogenation in the course of the IMPK reaction, a process not without precedence.[7b,14] This side reaction can be suppressed if the conversion is carried out in an O_2 atmosphere, but the total yield of the tricyclic product is decreased due to the partial decomplexation of the starting material. The cyclization of **38** over SiO_2 occurs more sluggishly and results in the formation of **42** as the major product (Scheme XII).

It is significant that, prior to this study,[15] not a single example of the IMPK reaction involving the participation of a conjugated double bond could be found among the numerous publications dealing with this reaction.[3b] To evaluate the scope of the applicability of this discovery, we studied the possibility of performing this transformation for some related acylmethoxy adducts. Interaction of **6** with **2** under standard conditions of acylmethoxyacylation gave the expected adducts **43a,b** in 85% yield (a mixture of diastereomers in a ratio of 2:1) (Scheme XIII). This mixture, when applied to the surface of Fluorisil, underwent a smooth IMPK reaction and gave a tetracyclic product **44** in good yield. The structure of the latter was unequivocally proven by single-crystal X-ray analysis. It was also shown that the individual isomers **43a** and **43b** were converted into the same product **44** with a comparable rate.

In a similar way, reaction of **28** with **2** gave adducts **46a,b** in nearly quantitative yield (a:b = 1:3, Scheme XIV). Trial experiments reveal that only isomer **46a**, obviously with a cis orientation of the ethynyl and acyl substituents is able to undergo an IMPK reaction (both under DSAC and LPC), while **46b** can

Scheme XIV



be recovered intact (cf. with the data in Schemes X and XI). In a preparative run with a mixture of **46a,b**, the respective tetracyclic product **47** was obtained as a single isomer in ca. 70% yield (calculated for the content of reactive isomer **46a** in the initial mixture) (Scheme XIV). In this case, no methanol elimination was observed. The recovered **46b** could be equilibrated into the same 1:3 mixture of **46a,b** upon treatment with BF_3 in CH_2Cl_2 at −75 °C (MeOH quench, yield ca. 85%). The structure of **47** was established by single-crystal X-ray analysis.

The attempts to carry out the IMPK reaction with several other Ad_E adducts like **8** or **15** failed. At best, only trace amounts of the respective tricyclic products were identified in the reaction mixtures. It seems reasonable to speculate that the increased propensity of **38**, **43**, and **46a** to undergo the IMPK reaction is related to the presence of the additional substituents at the α-atom of the double bond, which may serve as a factor restricting the conformational mobility of the side chain in such way that the double bond becomes more proximate to the reacting Co-complexed moiety.[16] These limitations notwithstanding, the reaction sequences shown in Schemes XII–XIV offer some promising options for the preparation of the polycyclic compounds useful for the synthesis of various polyquinanes.[6a,b] Thus, the tetracyclic compound **44**, which was prepared in two operationally simple steps from readily available precursors, contains the basic BCDE rings framework present in the structure of retigeranic acid **45**.[17] Pathways leading to the synthesis of the latter compound, via an approach similar to that shown in Scheme XIII, are being actively pursued in our group. It is also to be emphasized that the natural tetraquinane crinipellin-B (**48**)[18] contains the same tetracyclo-[6.6.0.$0^{1,11}$.$0^{3,7}$]tetradecane skeleton as the adduct **47**. Prior to our studies, this framework had never been synthesized, and only recently some models containing this system were prepared by a multistep reaction sequence.[18]

Summary. The results presented clearly indicate the viability of the approach suggested earlier[4a,5] as a general and practical route for the synthesis of polycyclic compounds.

The short sequence of transformations leading from available starting materials to rather complicated polycyclic compounds

(14) See also, for example: Montana, A. M.; Moyana, A.; Pericas, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995.

(15) Veretenov, A. L.; Smit, W. A.; Vorontsova, L. G.; Kurella, M. G.; Caple, R.; Gybin, A. S. *Tetrahedron Lett.* **1991**, *32*, 2109.

(16) One of the reviewers suggested that "perhaps the reason why the normal Pauson–Khand products are formed in Smit's case are (1) opposite polarization of the alkene compared to other intermolecular examples that yield dienes, and (2) no β-hydrogen is present to be removed after the cycloaddition". While this explanation also seems to be feasible, we believe that the final assessment of the relative importance of various factors affecting the ease of this reaction cannot be made on the basis of the available experimental data related to a rather limited set of the substrate structures.

(17) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.

(18) Mehta, G.; Srinivas Rao, K.; Sreenivasa Reddy, M. *J. Chem. Soc., Perkin Trans.* **1991**, 693 and references cited therein.

seems to be unprecedented. In general, it involves only three reactions: (i) Ad_E acylmethoxylation of the double bond of DCHCC of conjugated enynes leading to the formation of DCHCC of 1,6-enynes; (ii) transformation of the carbonyl group of these adducts; and (iii) IMPK reaction. For several model systems this sequence can be reduced to only two reactions, i and iii.

The stepwise Ad_E reaction used at the beginning of this sequence represents a fairly general protocol for the assemblage of the basic 1,6-enyne moiety which can thus be incorporated within various structural surroundings. The flexibility of this reaction is well established by the previously shown opportunities to vary the nature of all three building blocks utilized in this process, namely, 1,3-enynes, acylium electrophiles, and to a lesser extent, nucleophiles.[1,2,4] Therefore, the synthesis of structurally different precursors bearing this fragment can be reached along a unified and a convergent route. It is noteworthy that in the previously described preparations of bi- and tricyclic compounds, which included utilization of the IMPK reaction at the ring-forming step, the synthesis of the utilized 1,6-enyne precursors usually required rather long and tedious procedures.[19]

The second reaction involving 1,2-reduction of a carbonyl group in conjugation with a double bond is, essentially, an auxiliary step necessary to transform initial Ad_E products into substrates amenable to IMPK cycloaddition. One can easily envisage, however, the constructive utilization of this operation, e.g., via the use of functionally substituted Grignard reagents. Also fortunate is that, at least in some cases, this step can be avoided completely.

The final step of the described approach is based on the well-known IMPK reaction. The use of this reaction for the syntheses of angularly fused tricyclics has already been described.[9a-c] The data given in this paper provide additional evidence concerning the scope and stereochemistry of the process. An application of the IMPK reaction for the synthesis of linearly fused tricyclic compounds from monocyclic precursors had never been reported. Our data demonstrated the special efficiency of this approach for the preparation of the tricyclic [6.5.5] fused system with both trans and cis junctions of the [6.5] system, depending on the stereochemistry of the precursors. The IMPK cyclization in this series proceeds in a highly stereoselective manner. Less promising results were obtained in the [5.5.5] series. Here the cyclization of precursors with cis-oriented reacting moieties can be performed very efficiently (albeit with a low stereoselectivity). However the problem of securing the required stereochemistry in the course of the preparation of these precursors turned out to be nontrivial, and additional studies are necessary to solve this problem.

The opportunity to create tetracyclic systems by a simple tandem sequence of Ad_E plus IMPK reactions described above deserves special mention as a novel and a very prospective convergent route to various natural compounds, and the ramifications of this finding are currently under intensive study.

Some of the observed limitations of the suggested approach also seem to be worth mentioning. The most serious refers to the low stereoselectivity observed in some of the IMPK reactions. However, it seems justified to hope that modifications of the structures of the reactants and/or of the reaction conditions may provide some opportunities to avoid or at least to mollify these complications.[20]

It seems also relevant to comment that the syntheses of the tri- and tetracyclic systems described in this paper are based on the sequential and controlled functionalization of the starting 1,3-enyne system, which is eventually used as the synthetic equivalent of a tetradentate synthon. In these sequences the Co–carbonyl moiety is utilized as a multipurpose group which ensures protection of the triple bond at the initial step of electrophilic attack at the double bond and stabilization of the incipient carbocationic intermediate[21] and finally serves as a reacting function in the cyclization step at the end of the sequence.

Some final remarks should be made about the observed effects of adsorption on the efficiency of [2 + 2 + 1] cycloadditions. In line with our previous observations,[7] DSAC turned out to be the procedure of choice for the reactions with **4a,b**, **10**, **11**, **35a**, **38**, and **44**, while in other examples LPC worked equally well. Similar beneficial effects of the utilization of DSAC on the course of the IMPK reaction[22] as well as on some other transition metal mediated cyclizations[23] have recently been reported. While some suggestions have been advanced to account for the observed phenomena,[7a,b,23] the latter is still little understood and at best can serve to attest to the necessity and promise of more detailed studies in this area.[24]

Experimental Section

General. ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer and the ^{13}C spectra on a Brucker MA-300 spectrometer for $CDCl_3$ solutions with TMS as an internal standard. Mass spectra were obtained on a Varian MAT CH-6 (70 eV). Determinations of exact mass were carried out with a JMS D-300. Microanalyses were performed on a Perkin-Elmer 240 instrument by the Analytical Department of the Zelinsky Institute of Organic Chemistry. The analytical TLC plates used were Silufol UV-active silica gel on aluminum foil (Czechoslovakia). Unless specified, preparative isolation and separation of isomers were achieved on plates 22 × 24 cm with unfixed SiO_2 (LSL 40/100 μm or Silpearl, both from Czechoslovakia, 2 mm layer, PTLC). DCHCC of acetylenic compounds were prepared by the treatment of appropriate precursors with $Co_2(CO)_8$ as described elsewhere (e.g., data in ref 4d). DCHCC **6** and **28** were prepared by the dehydration of DCHCC of 1-ethynyl-1-hydroxycyclohexene and -cyclopentene, respectively, in accordance with the following general procedure. To a stirred solution of the starting carbinol (10 mmol) in CH_2Cl_2 was added freshly distilled $BF_3{\cdot}Et_2O$ (0.45 g, 4 mmol) at 20 °C. The mixture was stirred for an additional 5 min and then quenched by Et_3N (0.45 g, 4.5 mmol) and filtered through SiO_2 (3 mm). After removal of the solvent, the residue was dissolved in pentane or ether and separated from the traces of black precipitate by additional filtration through SiO_2. Removal of the solvent under reduced pressure gave practically pure complex **6** or **28** in nearly quantitatively yield (90–95%) from the corresponding conjugated enynes. Oxidative decomplexation of DCHCC was carried out with $Ce(NH_4)_2(NO_3)_6$ by the modified procedure[2a] as follows. $Ce(NH_4)_2(NO_3)_6$ (2.74 g, 5 mmol) was dissolved in acetone (6 mL) and cooled down to −30 to −35 °C. A solution of DCHCC (1 mmol) in acetone (1 mL) was added, and after 5 min the mixture was quenched with ether–water (50 mL, 5:1). The ethereal layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave the corresponding adducts in nearly quantitative yields. Unsaturated acyl fluorides used for the generation of acylium cations **2**, **7**, and **14** were prepared by the dictillation of the respective chlorides over anhydrous ZnF_2;[4c,d] 3-chloropropionyl fluoride and 2-methyl-3-chloropropionyl fluoride used as the precursors for the generation of **16** and **22**, respectively, were obtained by reaction of the respective acyl chlorides with liquid HF in accordance with a general procedure described earlier.[25] Acyl fluorides were purified by distillation (yields 60–80%) and stored over anhydrous NaF in the freezer. Electrophilic agents, acylium tetrafluoroborates, were generated in situ by interaction of respective acyl fluorides with an excess of gaseous BF_3

(19) Compare with the procedures described in ref 9a,b. See also: (a) MacWhorter, S. E.; Schore, N. E. *J. Org. Chem.* **1991**, *56*, 338. (b) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. (c) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *24*, 5861. (d) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 338. (e) Castro, J.; Sorensen, H.; Riera, A.; Morin, A.; Moyano, A.; Pericas, M. A.; Green, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388 and references cited in these publications.

(20) While there is no general solution to the problem of control over the stereoselectivity of the IMKP reaction, several possible options are suggested, as mentioned in ref 3b. For recent data, see: (a) Poch, M.; Valenti, E.; Moyano, A.; Pericas, M. A.; Castro, J.; DeNicola, A.; Green, A. E. *Tetrahedron Lett.* **1990**, *31*, 7505. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *37*, 5289.

(21) For the properties of Co-stabilized propargyl cationic species, see a review: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.

(22) (a) Jeong, N.; Yoo, S.; Lee, S. J.; Lee, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1991**, *32*, 2137. (b) Roush, W. R.; Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285. (c) Smit, W. A.; Kireev, S. L.; Nefedov, O. M.; Tarasov, V. A. *Tetrahedron Lett.* **1991**, *32*, 4021. (d) Brown, S. W.; Pauson, P. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1205.

(23) Katz, T. J.; Yang, G. X. *Tetrahedron Lett.* **1991**, *32*, 5895.

(24) For a general survey of surface-promoted reactions, see: *Preparative Chemistry Using Supported Reagents*; Laszlo, P., Ed.; Academic Press: New York, 1987.

(25) Olah, G. A.; Comissarov, M. B. *J. Am. Chem. Soc.* **1966**, *88*, 4442.

introduced by a syringe. All reactions were conducted under an argon atmosphere.

$Co_2(CO)_6$ Complex of 3-Methoxy-5-(cyclopent-1′-en-1′-yl)pent-1-yn-5-one (3). To a stirred solution of DCHCC of vinylacetylene **1** (0.76 g, 2.25 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added 1-cyclopentenoyl fluoride (0.34 g, 3.0 mmol) and then gaseous BF_3 was introduced (200 mL, ca. 8 mmol). The mixture was stirred until TLC monitoring indicated complete disappearance of the starting material (10 min), quenched with absolute MeOH (5 mL), warmed up to −40 °C, and poured into a stirred mixture of aqueous $NaHCO_3$–ether. After separation and additional extraction with ether, the organic layer was thoroughly washed with aqueous $NaHCO_3$ and water and dried over Na_2SO_4. Solvent evaporation gave practically pure **3** (TLC, ^1H NMR) as a dark red oil (1.03 g, 98%, R_f = 0.35, benzene), which was used without additional purification. To ascertain the structure, a portion of **3** was decomplexed (Ce^{4+}, see above; yield 95%) into 3-methoxy-5-(cyclopent-1′-en-1′-yl)-pent-1-yn-5-one (**3a**): ^1H NMR 6.78 (1 H, m), 4.49 (1 H, ddd, J = 2.2, 5.0, 8.0 Hz), 3.4 (3 H, s), 3.2 (1 H, dd, J = 8.0, 16.0 Hz), 2.9 (1 H, dd, J = 5.0, 16.0 Hz), 2.46 (1 H, d, J = 2.2 Hz), 2.55 (4 H, m), 1.9 (2 H, m).

$Co_2(CO)_6$ Complex of 3-Methoxy-5-(cyclopent-1′-en-1′-yl)pent-1-yn-5-ol (4). To a stirred solution of **3** (0.83 g, 1.8 mmol) in MeOH (18 mL) were added sequentially $CeCl_3 \cdot 7H_2O$ (0.69 g, 1.85 mmol) and, after the mixture was cooled down to −50 °C, $NaBH_4$ (0.076 g, 2 mmol). After 5 min, ether (50 mL) was added, the reaction mixture was filtered through SiO_2, and the solvent was removed. The residue was dissolved in ether (20 mL) and again filtered through SiO_2. Removal of the solvent and separation of the residue (PTLC, eluent $CHCl_3$–Et_2O, 20:1) gave individual **4a** (0.47 g, 56%) and **4b** (0.31 g, 37%) as red-purple liquids (R_f = 0.50 and 0.41, respectively, both C_6H_6–Et_2O, 6:1), MS m/e 298 (M^+ − 6CO) (for both isomers). For identification, samples of **4a** and **4b** were converted (by oxidative decomplexation) into respective metal-free **4aa** and **4ba** (yields > 90%).

For **4aa**: ^1H NMR 5.63 (1 H, m), 4.53 (1 H, m), 4.18 (1 H, ddd, J = 2.2, 5.0, 7.0 Hz), 3.42 (3 H, s), 2.48 (1 H, d, J = 2.2 Hz), 2.3 (4 H, m), 1.9 (4 H, m). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.45; H, 8.79. For **4ba**: ^1H NMR 5.63 (1 H, m), 4.48 (1 H, dd, J = 4.3, 9.0 Hz), 4.16 (1 H, ddd, J = 2.2, 6.0, 8.0 Hz), 3.43 (3 H, s), 2.50 (1 H, d, J = 2.2 Hz), 2.3 (4 H, m), 2.03 (1 H, ddd, J = 14.0, 6.0, 4.3 Hz), 1.95 (1 H, dd, J = 14.0, 9.0, 8.0 Hz), 1.88 (4 H, m). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.57; H, 8.82.

4-Methoxy-2-hydroxytricyclo[6.3.0.0^{1,5}]undec-5-en-7-one (5). Chromatography grade silica gel (Silpearl, 5 g, 100–120 μm, Chemapol, Czechoslovakia,[26] water content ca. 15%) was added to the solution of **4a** (0.57 g, 1.22 mmol) in hexane–ether (20 mL, 1:1). After removal of the solvent on a rotovap, the orange powder was kept under vacuum for 10 min, and the reaction vessel was flushed with Ar. This procedure was repeated three times to remove traces of oxygen. The vessel was sealed and heated at 100 °C for 1 h (conditions required for the complete consumption of the starting material, TLC control). The resulting gray powder was washed with ether (2 × 25 mL) and methanol (3 × 25 mL). After solvent removal, the brown residue (0.338 g) was chromatographed to give a mixture **5a,b** (0.103 g, yield 41%) as a colorless oil (**5a**:**5b** = 3:5, ^1H NMR), MS m/e 208 (M^+) (for both). This mixture was further separated by PTLC (Silpearl, elution with ether, three runs) into individual **5a** and **5b** (R_f = 0.49 and 0.45, ether, respectively). **5a**: colorless plates, mp 128–129 °C (pentane). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.07; H, 7.82. **5b**: colorless oil. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 68.92; H, 7.63. ^1H and ^{13}C NMR data for **5a,b** are given in Tables I and II. The structure of **5a** as (1*R**,2*S**,4*S**,8*R**)-4-methoxy-2-hydroxytricyclo[6.3.0.0^{1,5}]undec-5-en-7-one was established by X-ray analysis.

A mixture of stereoisomers **5c,d** was obtained similarly upon the cyclization of **4b** (0.65 g, 1.39 mmol) on SiO_2 (5.5 g). Separation of this mixture by PTLC (vide infra) produced individual isomers as colorless liquids, **5c** (0.046 g, yield 16%, R_f = 0.68, ether), and **5d** (0.042 g, yield 14%, R_f = 0.56, ether). **5c**: Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 68.89; H, 7.58. **5d**: Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 68.80; H, 7.50.

$Co_2(CO)_6$ complex of (1*R,2*R**)-1-methoxy-1-ethynyl-2-[(*E*)-1′-oxobut-2′-enyl]cyclohexane (8)** was prepared as described above for **3** from DCHCC of 1-ethynylcyclohexene **6** (2.16 g, 5.5 mmol), crotonoyl fluoride (0.97 g, 11 mmol), and BF_3 (413 mL, 16.5 mmol). PTLC gave **8** as a dark red oil, 1.41 g (yield 52%).[10] The product was used without additional purification.

(1*R,2*R**)-1-Methoxy-1-ethynyl-2-[(*E*)-1′-oxobut-2′-enyl]cyclohexane (9)** was prepared by oxidative decomplexation of **8** (vide infra): yield 92%, colorless oil; ^1H NMR 6.86 (1 H, dq, J = 6.9, 15.5 Hz), 6.34 (1 H, dq, J = 1.8, 15.5 Hz), 3.34 (3 H, s), 2.83 (1 H, dd, J = 3.8, 11.0 Hz), 2.64 (1 H, s), 1.87 (3 H, dd, J = 1.8, 6.9 Hz), 1.2–2.3 (m, 8 H). The identity of **9** was ascertained by comparison (TLC, ^1H NMR) with an authentic sample as described earlier.[2a]

(1*R,2*R**,1′*R*)-1-Methoxy-1-ethynyl-2-[(*E*)-1′-hydroxybut-2′-en-1′-yl]cyclohexane (10)** was prepared from **9** as outlined above for **4a,b**, but the reaction was carried out at 0–5 °C. Reduction of **9** (0.54 g, 2.6 mmol) gave **10** (0.49 g, yield 91%). Only one diastereomer was formed (^1H and ^{13}C NMR data), and it was used without additional purification: ^1H NMR 5.8–5.5 (2 H, m), 4.65 (1 H, m), 3.41 (3 H, s), 2.71 (1 H, s), 2.23 (1 H, ddt, J = 1.6, 3.3, 11.9 Hz), 1.7 (3 H, dt, J = 1.8, 6 Hz), 1.1–1.8 (9 H, m); ^{13}C NMR 132.8 (C-2′), 125.1 (C-3′), 83.4 (C-7), 78.1 (C-1′), 76.3 (C-1), 71.8 (C-8), 52.5 (C-2), 50.5 (MeO), 37.0, 25.5, 23.5, 23.1 (C-3–C-6), 17.5 (C-4′); MS m/z 208 (M^+).

(1*R,2*R**,1′*R*)-1-Methoxy-1-ethynyl-2-[(*E*)-1′-acetoxybut-2′-en-1′-yl]cyclohexane (11).** A mixture of **10** (0.49 g, 2.36 mmol), Ac_2O (0.72 g, 7.05 mmol), Et_3N (0.71 g, 7.05 mmol), and 4-DMAP (0.02 g) was stirred at 20 °C for 40 min. Et_2O (70 mL) was added, and the mixture was washed with 3% aqueous HCl, water, $NaHCO_3$, (3 × 25 mL), and water and dried over Na_2SO_4. Removal of the solvent gave individual **11** (0.548 g, yield 93%) as colorless crystals: mp 86–87 °C (hexane); ^1H NMR 5.84 (1 H, m), 5.64 (1 H, ddq, J = 15.4, 6.3, 1.1 Hz), 5.43 (1 H, ddq, J = 15.4, 6.2, 2.0 Hz), 3.37 (3 H, s), 2.48 (1 H, s), 2.23 (1 H, ddt, J = 12.1, 3.2, 1.5 Hz), 2.02 (3 H, s), 1.68 (3 H, dt, J = 6.3, 2.0 Hz), 1.1–1.8 (8 H, m); MS m/z 250 (M^+); exact mass found M^+ 250.1576, $C_{15}H_{22}O_3$ requires 250.1569. The structure was proven by X-ray analysis.

10-Methyl-8-hydroxy-2-methoxytricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-one (12a,b). $Co_2(CO)_8$ (0.75 g, 2.19 mmol) was added to a stirred solution of **10** (0.416 g, 2.0 mmol) in Et_2O (15 mL) at 20 °C. After 45 min the evolution of CO ceased. The dark red solution was mixed with SiO_2 (Silpearl, 120–140 μm, water content ca. 10%, 12.5 g), the solvent was removed under reduced pressure, and the red powder was heated at 50 °C for 4 h. The silica gel was washed with Et_2O (6 × 25 mL), and the residue, after solvent removal, was chromatographed on SiO_2 to give a small amount of the starting material **10** (0.087 g, yield 9%) and a mixture of **12a,b** (0.41 g, semicrystalline solid, yield 87%, R_f = 0.39 (ether), a:b = 3.8:1, ^1H NMR). Recrystallization from benzene–hexane (1:1) gave 0.238 g of the 2*R**,7*S**,8*R**,9*S**,10*S** isomer **12a**, colorless crystals, mp 97–98 °C (hexane–ether), and 0.16 g of the mixture **12a,b**, MS m/e 236 (M^+), 204 (M^+ − MeOH) (for both). For **12a**, exact mass found M^+ 236.1419, $C_{14}H_{20}O_3$ requires 236.1412; NMR spectra, see Tables III and IV. The cyclization of **10** under LPC (hexane, 60 °C, 2 h, complete conversion of **10**) gave the same mixture **12a,b** in 39% yield.

10-Methyl-8-acetoxy-2-methoxytricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-one (13) was obtained as a mixture of stereoisomers **13a,b** by the cyclization of **11** (0.21 g) on SiO_2 (60 °C, 0.5 h) in 73% yield (R_f = 0.53, ether, a:b = 3.3:1, ^1H NMR), which were separated by PTLC into individual **13a** (R_f = 0.5, ether) and **13b** (R_f = 0.55, ether). For NMR spectra, see Tables III and IV. **13a**: MS m/e 278 (M^+); exact mass found M^+ 278.1511, $C_{16}H_{22}O_4$ requires 278.1518. **13b**: MS m/e 278 (M^+), 218 (M^+ − CH_3COOH).

The identity of the products was additionally ascertained by ^1H NMR comparison with authentic samples prepared by acetylation of **12a** and **12b**.

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-(1′-oxoprop-2′-enyl)-cyclohexane (15) was prepared as described above for **3** from **6** (0.39 g, 1 mmol), acryloyl fluoride (0.22 g, 3 mmol), and BF_3 (125 mL, 5 mmol). After TLC separation, **15** (0.11 g, yield 24%, R_f = 0.61, hexane–ether, 10:1) was obtained as a dark red liquid. ^1H NMR spectra of the decomplexed product **16** indicated the presence of two stereoisomers in a ratio of ca. 8:1. For the major 1*R**,2*R** of isomer **16a**: ^1H NMR 6.58 (1 H, dd, J = 17.1, 9.0 Hz), 6.22 (1 H, dd, J = 17.1, 2.8 Hz), 5.66 (1 H, dd, J = 9.0, 2.8 Hz), 3.35 (3 H, s), 2.89 (1 H, dd, J = 10.9, 3.3 Hz), 2.63 (1 H, s), 2.29 (1 H, m), 1.2–1.8 (7 H, m).

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-(3′-chloro-1′-oxopropyl)cyclohexane (18a,b) was prepared from **6** (1.24 g, 3.1 mmol), 3-chloropropanoyl fluoride (0.86 g, 7.9 mmol), and BF_3 (355 mL, 14.2 mmol) as was described for **3**. Removal of traces of **6** by filtration through a short column with SiO_2 gave **18a,b** as a dark red liquid (1.54 g, yield 95%, R_f = 0.55, hexane–ether, 10:1), which was further decomplexed into **19a,b** (yield 95%, a:b = 9:1, ^1H NMR). Major isomer **19a**: ^1H NMR 3.7 (2 H, m), 3.35 (3 H, s), 2.63 (1 H, s), 2.59 (1 H, dd, J = 8.2, 4.0 Hz), 2.26 (1 H, m), 1.2–1.8 (7 H, m); MS (mixture **19a,b**) m/z 230, 228 (M^+), 215, 213 (M^+ − Me), 199, 197 (M^+ − MeO), 193 (M^+ − Cl). The mixture was used without additional purification.

1-Methoxy-1-ethynyl-2-(1′-oxoprop-2′-enyl)cyclohexane (16a,b). A solution of **19a,b** (0.64 g, 2.8 mmol) in pentane (10 mL) was mixed with base Al_2O_3 (Woelm, 5 g). The solvent was removed on a rotovap, and

(26) The use of silica gels of different brands (e.g., Aldrich, 70–230 mesh, 60 Å) leads to comparable results (see, also data in ref 7b,c).

the dry powder was left at ambient temperature for an additional 10 min. Washing of the sorbent with ether gave **16a,b** as a slightly yellow liquid (0.48 g, yield 89%, R_f = 0.61, hexane–ether, 1:3, ratio a:b = 12:1, ^{1}H NMR). The ^{1}H NMR spectrum of the product is almost superimposable with that of the sample described above, the only difference being due to variation in the a:b ratio; MS (for the mixture) *m/e* 194 (M^+). The product was immediately used in further reactions without any additional purification.

1-Methoxy-1-ethynyl-2-(1′-hydroxyprop-2′-en-1′-yl)cyclohexane (20a) was prepared as was described for **10** from **16a,b** (0.48 g, 2.5 mmol). The crude product (0.45 g, yield 87%) contained three stereoisomers in the ratio 9:1.6:1 (^{1}H NMR). Column chromatography on SiO_2 (eluent hexane–ether, 25:1) gave **20a** (0.33 g, yield 67%, R_f = 0.55, hexane–ether, 3:1) as a colorless liquid: ^{1}H NMR 5.81 (1 H, ddd, *J* = 17.3, 10.8, 5.0 Hz), 5.22 (1 H, dt, *J* = 17.3, 1.9 Hz), 5.05 (1 H, dt, *J* = 10.8, 1.9 Hz), 4.70 (1 H, m), 3.37 (3 H, s), 2.69 (1 H, s), 2.19 (1 H, m), 1.0–1.8 (8 H, **m**). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.89; H, 9.20.

8-Hydroxy-2-methoxytricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-one (21), Product **20a** was converted into the respective $Co_2(CO)_6$ complex via a conventional treatment with $Co_2(CO)_8$. Cyclization of this complex (0.48 g, 1 mmol) under DSAC (SiO_2, 55 °C, 4 H) gave the mixture of **21a** and **21b** in ca. 65% yield. PTLC afforded pure **21a** (0.089 g, yield 40%, R_f = 0.54, hexane–ether, 3:1) and **21b** (0.047 g, yield 21%, R_f = 0.64, hexane–ether, 3:1) as colorless liquids. Similar cyclization (0.478 g, 1 mmol) under LPC (ether, 5 mL, 50 °C, 10 h, sealed vessel) gave a mixture of **21a,b** in ca. 70% yield in the ratio 1:1. Pure **21a** and **21b** were isolated in 32% and 31% yields, respectively; MS (for both isomers) *m/e* 222 (M^+), 190 (M^+ – MeOH). For ^{1}H NMR data, see Tables III and IV. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.03; H, 8.05 (**21a**); C, 69.90; H, 7.95 (**21b**).

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-(2′-methyl-3′-chloro-1′-oxopropyl)cyclohexane (23) was prepared as described for **3** from **6** (1.72 g, 4.4 mmol), 2-methyl-3-chloropropanoyl fluoride (1.1 g, 10.9 mmol), and BF_3 (490 mL, 19.5 mmol). After the removal of traces of the starting material, the crude product **23a–d** (2.19 g, yield 94%, R_f = 0.56, hexane–ether, 10:1) was decomplexed into **24a–d**. ^{1}H NMR spectra of the latter revealed general patterns similar to those observed in **18a,b** and confirmed the presence of four components in the ratio 3:2:1:1; MS (for the mixture) *m/e* 243, 241 (M^+), 228, 226 (M^+ – Me), 212, 210 (M^+ – MeO), 206 (M^+ – Cl). No attempts were made to separate the isomers, and the mixture was immediately used for further transformations.

1-Methoxy-1-ethynyl-2-(2′-methyl-1′-oxoprop-2′-enyl)cyclohexane (25a,b) was prepared by dehydrochlorination of the above mixture under the conditions described for **16a,b**. Upon this treatment, **24a–d** (0.97 g, 4 mmol) gave a mixture of stereoisomers **25a,b**, which was separated by column chromatography on SiO_2 (hexane–ether, 40:1) into the individual isomers **25a** (0.21 g, yield 25%, R_f = 0.22) and **25b** (0.61 g, yield 74%, R_f = 0.26, hexane–ether, 10:1); MS *m/e* (for both isomers) 206 (M^+), 191 (M^+ – Me), 174 (M^+ – MeOH).

25a: ^{1}H NMR 5.91 (1 H, br s), 5.72 (1 H, br s), 3.30 (1 H, m), 3.28 (3 H, s), 2.61 (1 H, s), 2.23 (1 H, m), 1.85 (3 H, s), 1.1–1.8 (7 H, m); MS *m/e* 206 (M^+), 191 (M^+ – Me), 174 (M^+ – MeOH). **25b**: ^{1}H NMR 5.89 (1 H, br s), 5.70 (1 H, br s), 3.64 (1 H, t, *J* = 5.2 Hz), 3.29 (3 H, s), 2.51 (1 H, s), 2.30 (1 H, m), 1.86 (3 H, s), 1.1–1.8 (7 H, m). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.43; H, 8.65 (**25a**); C, 75.42; H, 8.70 (**25b**).

1-Methoxy-1-ethynyl-2-(1′-hydroxy-2′-methylprop-2′-en-1′-yl)cyclohexane (26) was prepared as was described above for **10**. Reduction of **25a** (0.41 g, 2 mmol) gave a mixture of stereoisomers, which was separated by chromatography on SiO_2 (hexane–ether, 30:1) into individual **26a** (0.08 g, yield 20%, R_f = 0.34, hexane–ether, 3:1) and **26b** (0.25 g, yield 60%, R_f = 0.25, hexane–ether, 3:1). Similarly, individual **26c** (0.32 g, yield 60%, R_f = 0.27, hexane–ether, 3:1) and **26d** (0.08 g, yield 15%, R_f = 0.40, hexane–ether, 3:1) were prepared starting from **25b** (0.53 g, 2.6 mmol). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.66. Found: C, 74.70; H, 9.58 (**26b**); C, 74.76; H, 9.53 (**26c**).

26a: ^{1}H NMR 4.86 (1 H, m), 4.84 (1 H, m), 4.68 (1 H, br s), 3.38 (3 H, s), 2.71 (1 H, s), 1.67 (3 H, br s), 1.0–1.8 (9 H, m). **26b**: ^{1}H NMR 4.86 (1 H, m), 4.83 (1 H, m), 4.28 (1 H, d, *J* = 9.6 Hz), 3.42 (3 H, s), 2.66 (1 H, s), 2.28 (1 H, m), 1.69 (3 H, br s), 1.0–1.8 (8 H, m). **26c**: ^{1}H NMR 4.89 (1 H, m), 4.82 (1 H, m), 4.38 (1 H, d, *J* = 8.8 Hz), 3.37 (3 H, s), 2.64 (1 H, s), 1.68 (3 H, br s), 1.2–2.0 (9 H, m). **26d**: ^{1}H NMR 5.06 (1 H, m), 4.90 (1 H, m), 4.81 (1 H, m), 3.35 (3 H, s), 2.57 (1 H, s), 2.29 (1 H, m), 1.66 (3 H, br s), 1.1–2.0 (8 H, m).

9-Methyl-8-hydroxy-2-methoxytricyclo[7.3.0.0^{2,7}]dodec-1(12)-en-11-one (27). Alcohols **26a–c** were converted into their respective $Co_2(CO)_6$ complexes, and the latter underwent IMPK cyclization under the conditions indicated below. Stereoisomers of the cyclized products were separated by PTLC (ether).

27a,b. From **26a** (0.21 g, 1 mmol) under LPC (ether, 50 °C, 6 H), **27a** (0.123 g, yield 52%, R_f = 0.48, ether) and **27b** (0.016 g, yield 7%, R_f = 0.79, ether) were obtained. **27a**: MS *m/e* 236 (M^+); exact mass found 236.1416, $C_{14}H_{20}O_3$ requires 236.1412. **27b**: MS *m/e* 236 (M^+), 221 (M^+ – Me).

27c. From **26b** (0.21 g, 1 mmol) under LPC (ether, 50 °C, 7 h), **27c** (0.161 g, yield 68%, R_f = 0.67, ether) was obtained: MS *m/e* 236 (M^+); exact mass found 236.1410, $C_{14}H_{20}O_3$ requires 236.1412.

27d,e. From **26c** (0.21 g, 1 mmol) under LPC (ether, 60 °C, 8 H), **27d** (0.111 g, yield 47%, R_f = 0.20, hexane–ether, 2:1) and **27e** (0.016 g, yield 7%, R_f = 0.25, hexane–ether, 0.25) were obtained. A similar reaction under DSAC (SiO_2, 70 °C, 10 h) gave the same products **27d** and **27e** in 53% and 5% yields, respectively. A major part of the **27d** was isolated by the recrystallization from ether–pentane, 1:2. Separation of the mother liquor by PTLC gave additional amounts of **27d** and **27e** in admixture with **27d**. **27d**: mp 160–161 °C. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.04; H, 8.52. **27e**: MS *m/e* 236 (M^+), 221 (M^+ – Me).

27f. From **26d** (0.21 g, 1 mmol) under LPC (ether–pentane, 1:1, 10 mL, 60 °C, 7 h), **27f** (0.184 g, yield 78%, R_f = 0.56, ether) was obtained. HRMS: calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1408. For ^{1}H and ^{13}C NMR data of **27a,c,d,f**, see Tables III and IV.

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-[(*E*)-1′-oxobut-2′-enyl]cyclopentane (29) was prepared as described earlier for **3** from **28** (3.4 g, 9.0 mmol), crotonyl fluoride (1.47 g, 15 mmol), and BF_3 (650 mL, 26 mmol). After PTLC, **29** (2.60 g, yield 59%, R_f = 0.25, benzene) was isolated as a deep red liquid. The less polar fraction consisted of the *Z* isomer (0.43 g, yield 11%, R_f = 0.3, benzene). Its structure was ascertained by MS and ^{1}H NMR spectra of the decomplexed material. Only the *E* isomer of **29** was used for further conversions. Oxidative decomplexation of **29** gave (1*R**,2*S**)-1-methoxy-1-ethynyl-2-[(*E*)-1′-oxobut-2′-enyl]cyclopentane (**30**) (yield 95%, mp 62–63 °C, pentane): MS *m/e* 192 (M^+); exact mass found M^+ 192.1153, $C_{12}H_{16}O_2$ requires 192.1150; ^{1}H NMR 6.9 (1 H, dq, *J* = 16, 7 Hz), 6.55 (1 H, dq, *J* = 16, 1.5 Hz), 3.44 (1 H, t, *J* = 8 Hz), 3.28 (3 H, s), 2.68 (1 H, s), 1.9 (3 H, dd, *J* = 7, 1.5 Hz), 1.6–2.4 (6 H, m). The structure of **30** as the 1*R**,2*S** isomer was unambiguously proven by X-ray data.

1-Methoxy-1-ethynyl-2-[(*E*)-1′-hydroxybut-2′-enyl]cyclopentane (31) was prepared as described above for **10**. From **30** (0.15 g, 0.79 mmol), a mixture of **31a,b** (0.143 g, yield 93%) was prepared. PTLC (column, hexane–ether, 2:1) gave individual **31a** (0.062 g, R_f = 0.45, hexane–ether, 2:1) and **31b** (0.075 g, R_f = 0.39, hexane–ether, 2:1).

31a: ^{1}H NMR 5.68 (1 H, dq, *J* = 16, 6.5 Hz), 5.50 (1 H, ddq, *J* = 16, 11, 1.6 Hz), 4.2 (1 H, t, *J* = 11 Hz), 3.36 (3 H, s), 2.61 (1 H, s), 1.66 (3 H, dd, *J* = 6.5, 1.6 Hz), 1.5–2.2 (7 H, m); MS *m/z* 194 (M^+). **31b**: ^{1}H NMR 5.67 (1 H, dq, *J* = 15.5, 7 Hz), 5.55 (1 H, ddq, *J* = 16, 3, 1.6 Hz), 4.67 (1 H, br d, *J* = 11 Hz), 3.31 (3 H, s), 2.51 (1 H, s), 1.65 (3 H, dd, *J* = 7, 1.6 Hz), 1.6–2.3 (7 H, m); MS *m/z* 194 (M^+).

Attempted cyclization of Co-complexed **31a** and **31b** (SiO_2, 100 °C, 10 h, or hexane, 60 °C, 6 h, total conversion of the starting materials) did not produce even trace amounts of tricyclic products (MS data) and resulted in the formation of a mixture of no less than 4–5 products (TLC).

1-Methoxy-1-ethynyl-2-[(*E*)-1′-methyl-1′-hydroxybut-2′-en-1′-yl]-cyclopentane (32). A solution of MeMgI (8 mmol) in ether (10 mL) was added to **30** (0.585 g, 3.05 mmol) dissolved in ether (50 mL) at −55 °C. The reaction mixture was warmed up to −20 °C and, after 20 min, quenched with NH_4Cl–H_2O. After the usual workup and solvent removal, a colorless oil was obtained (0.506 g, yield 80%, R_f = 0.41, benzene–ether, 10:1), MS *m/e* 208 (M^+). The attempt to separate the isomers by PTLC failed. The proposed structure as a 1,2-adduct is based on the appearance of the novel high-field Me signals (at 1.12 and 1.30) and on the similarity of the general ^{1}H NMR spectral pattern to those observed for **31a,b**. The diastereoisomeric ratio was ca. 2:1 (from the integration of nonoverlapping MeO signals).

A mixture **32a,b** was converted into the respective Co complex, and the latter was applied to SiO_2 and heated at 60 °C for 1 h. All starting material was consumed (TLC), but analysis of the reaction mixture revealed the presence of no less than five compounds (^{1}H NMR), none of them being a tricyclic product (MS).

$Co_2(CO)_6$ Complex of 1-Methoxy-1-ethynyl-2-(3′-chloropropionyl)-cyclopentane (33). (i) Under Kinetically Controlled Conditions. Into a solution of **28** (3.4 g, 9.0 mmol) and 3-chloropropanoyl fluoride (0.88 g, 8 mmol) in CH_2Cl_2 (80 mL) at −70 °C was introduced gaseous BF_3 (300 mL, 12 mmol) with a syringe. The mixture was kept for 20 min at −70 °C, quenched by cooled MeOH (4 mL), and then immediately neutralized by the addition of pyridine (0.96 g, 12 mmol). After the usual treatment and PTLC, unreacted **28** (0.48 g, yield 14%) and **33a,b** (2.84 g, yield 63%, a:b = 1:1.1, from ^{1}H NMR of the decomplexed sample) were recovered.

(ii) **Under Thermodynamically Controlled Conditions.** The reaction was carried out as described above, the only difference being that prior to neutralization with pyridine the reaction mixture was kept at 20 °C for 30 min. The product was isolated in 60% yield and was shown to contain at least 95% (^{1}H NMR) of a single isomer **33b**: ^{1}H NMR (for the decomplexed sample of **33b**) 3.66 (2 H, m), 2.9–3.4 (3 H, m), 3.28 (3 H, s), 2.68 (1 H, s), 1.6–2.4 (6 H, m). Adducts **33a,b** were immediately used without additional purification.

1-Methoxy-1-ethynyl-2-(1′-oxoprop-2′-enyl)cyclopentane (34). Oxidative decomplexation with subsequent dehydrochlorination of **33b** over Al_2O_3 under the conditions described above for the preparation of **16a,b** gave **34b** as a single product, yield 85%: ^{1}H NMR 6.82 (1 H, dd, J = 17.0, 10.5 Hz), 6.3 (1 H, dd, J = 17.0, 1.5 Hz), 5.7 (1 H, dd, J = 10.5, 1.5 Hz,) 3.36 (1 H, m), 3.28 (3 H, s), 2.68 (1 H, s), 1.6–2.4 (6 H, m); MS m/e 178 (M^+). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.35; H, 8.15.

Similarly, from a mixture **33a,b** via oxidative decomplexation and dehydrochlorination, a mixture **34a,b** was formed (yield 90%, ratio a:b 1:1.2, ^{1}H NMR). The ^{1}H NMR spectrum of this ketone reveals the presence (in addition to the aforementioned signals of **34b**) the nonoverlapping signals of **34a**: 6.6 (1 H, dd, J = 17, 10.5 Hz), 6.2 (1 H, dd, J = 17, 1.5 Hz), 5.8 (1 H, dd, J = 10.5, 1.5 Hz), 3.40 (3 H, s), 2.54 (1 H, s); MS m/e 178 (M^+). This mixture was used for further reactions without separation of the isomers.

1-Methoxy-1-ethynyl-2-(1′-hydroxyprop-2′-en-1′-yl)cyclopentane 35. Reduction of **34b** under the conditions described above in the preparation of **10** gave a mixture of alcohols **35c,d** (yield 95%, c:d = 1.5:1, R_f = 0.64 and 0.72, chloroform–ether, 4:1), which were separated by PTLC.

35c: ^{1}H NMR 5.85 (1 H, ddd, J = 17.5, 10.5, 7.0 Hz), 5.25 (1 H, dd, J = 17.5, 1.5 Hz), 5.07 (1 H, dd, J = 10.5, 1.5 Hz), 4.65 (1 H, m), 3.31 (3 H, s), 1.4–2.1 (7 H, m); MS m/e 180 (M^+). **35d**: ^{1}H NMR 5.81 (1 H, ddd, J = 17.0, 10, 5 Hz), 5.29 (1 H, dt, J = 17.0, 2 Hz), 5.07 (1 H, dt, J = 10.5, 2 Hz), 4.76 (1 H, m), 3.36 (3 H, s), 2.53 (1 H, s), 1.6–2.21 (7 H, m); MS m/e 180 (M^+).

Both **35c** and **35d** were converted into respective Co complexes and subjected to the usual DSAC of the cyclization. No cyclic products were detected in the mixture of products formed after prolonged 1–5 h of heating at 60 °C (MS data).

Reduction of the mixture **34a,b** (0.257 g, 1.44 mmol) under the same conditions gave a mixture of four isomeric alcohols **35a–d** in 98% total yield. PTLC allowed the isolation of pure **35a** (0.089 g, yield 34%, R_f = 0.54, chloroform–ether, 4:1), **35d** (0.055 g, yield 22%, R_f = 0.64, chloroform–ether, 4:1), and **35c** (0.090 g, yield 36%, R_f = 0.72, chloroform–ether, 4:1). **35c,d** were identified by comparison (TLC, ^{1}H NMR) with the samples described above. No attempts were made to isolate pure isomer **35b**, identified by the presence of additional signals in the ^{1}H NMR spectrum of the initial mixture, ca. 3–5%. **35a**: ^{1}H NMR 5.87 (1 H, ddd, J = 17.5, 10.5, 5 Hz), 5.26 (1 H, dt, J = 17.5), 5.07 (1 H, dt, J = 10.5, 2 Hz), 4.58 (1 H, m), 3.31 (3 H, s), 2.69 (1 H, s), 1.6–2.1 (7 H, m). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.01; H, 8.85.

7-Hydroxy-2-methoxytricyclo[6.3.0.0^{2,6}]undec-11-en-10-ones 36. 35a (0.089 g, 0.494 mmol) was converted into the respective Co complex by treatment with $Co_2(CO)_8$ (0.186 g, 0.543 mmol) in pentane (5 mL) at 20 °C for 30 min. Then SiO_2 (Silpearl, 1.78 g, water content ca. 15%) was added to the solution, the solvent which was removed in vacuo, and the resulting powder was heated at 60 °C for 1 h. Washing with ether and removal of the solvent gave 0.095 g of oily residue. PTLC separation gave **36a** (0.038 g, yield 37%, R_f = 0.25, ether) and **36b** (0.036 g, yield 35%, R_f = 0.22, ether). For identification, both products were converted into the respective 7-acetoxy derivatives **37a** (mp 93–95 °C, pentane) and **37b** (mp 90–91 °C, pentane), as was described above for the preparation of **11**.

37a: ^{1}H NMR 6.01 (1 H, d, J = 2.5 Hz, H-11), 4.89 (1 H, d, J = 5.5 Hz, H-7), 3.28 (1 H, dddd, J = 7, 5.5, 3.5, 2.5 Hz, H-8), 3.19 (3 H, s, MeO), 2.72 (1 H, t, J = 9 Hz, H-6), 2.46 (1 H, dd, J = 18.5, 7 Hz, H-9), 2.28 (1 H, dd, J = 18.5, 3.5 Hz, H-9a), 2.01 (3 H, s, Ac), 1.45–2.25 (6 H, m). The structure was confirmed by X-ray analysis. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.98; H, 7.15. **37b**: ^{1}H NMR 6.07 (1 H, d, J = 2.5 Hz, H-11), 4.32 (1 H, dd, J = 9.5, 7 Hz, H-7), 3.38 (1 H, dddd, J = 9.5, 6, 3, 2.5 Hz, H-8), 3.21 (3 H, s, MeO), 2.71 (1 H, m, H-6), 2.65 (1 H, dd, J = 19, 3 Hz, H-9), 2.51 (1 H, dd, J = 19, 6 Hz, H-9a), 2.08 (3 H, s, Ac), 1.35–2.1 (6 H, m). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.80; H, 7.03.

9-Methyltricyclo[7.3.0.0^{2,7}]dodeca-1(12),2(7)-diene-8,11-dione (40), 9-Methyl-1-hydroxytricyclo[7.3.0.0^{2,7}]dodec-2(7)-ene-8,11-dione (41), and 9-Methyltricyclo[7.3.0.0^{2,7}]dodec-2(7)-ene-8,11-dione (42). To the solution of **23** (1.32 g, 2.5 mmol) in pentane (25 mL) was added Al_2O_3 (Woelm, basic, 13.2 g, water content ca. 15%). The solvent was removed on a rotovap, and oxygen was carefully stripped as described in the preparation of **5**. The residue was sealed and kept at 60 °C for 10 h. The resulting grayish powder was carefully washed with an EtOH–EtOAc mixture (30 mL, 1:5), and the solvent was removed. PTLC gave **40** (0.136 g, yield 27%), **41** (0.127 g, 23%), and **42** (0.020 g, yield 4%) as slightly colored liquids with R_f = 0.56, 0.10, and 0.42 (ether–hexane, 3:1), respectively. Similar products in the same ratio were formed by cyclization of **38** prepared from **25a,b**. Thermolysis of **38** (0.49 g, 1 mmol) on SiO_2 at 90 °C for 10 h gave, after similar treatment, **42** (0.1 g, yield 49%) and **40** (0.004 g, yield 2%) identical with the samples prepared above.

40: ^{1}H NMR 5.73 (1 H, s), 2.44 and 2.27 (2 H, pair of AB doublets, J = 17.0 Hz), 2.18–2.45 (4 H, m), 1.5–1.9 (4 H, m), 1.3 (3 H, br s); ^{13}C NMR 206.3 (C-11), 202.5 (C-8), 180.3 (C-1), 156.7 (C-2), 145.5 (C-7), 116.4 (C-12), 54.5 (C-9), 45.1 (C-10), 27.1 (Me at C-9), 23.8, 21.1, 20.9, 20.8 (C-3–C-6); MS m/e 202; exact mass found 202.0996, $C_{13}H_{14}O_2$ requires 202.0994. **41**: ^{1}H NMR 2.67 and 2.22 (pair of AA′BB′, dd, J = 19.0, 1.9, 1.6 Hz), 2.51 and 2.31 (pair of AA′BB′, dd, J = 19.3, 1.9, 1.6 Hz), 1.8–2.20 (4 H, m), 1.2–1.4 (4 H, m), 1.15 (3 H, br s); ^{13}C NMR 213.6 (C-11), 208.5 (C-8), 172.5 (C-2), 137.1 (C-7), 83.3 (C-1), 54.9 (C-9), 50.0 (C-12), 48.0 (C-10), 19.2 (Me at C-9), 22.7, 21.8, 21.3, 19.7 (C-3–C-6); MS m/e 220; exact mass found 220.1106, $C_{13}H_{16}O_3$ requires 220.1099. **42**: ^{1}H NMR 2.93 (1 H, m), 2.41 and 2.20 (pair of AA′BB′, dd, J = 19.2, 1.8, 1.7 Hz), 2.67 and 2.18 (pair of AA′BB′X, ddd, J = 18.6, 1.8, 1.7, 3.6, 10.6 Hz), 2.0–2.3 (4 H, m), 1.5–1.8 (4 H, m), 1.28 (3 H, br s); ^{13}C NMR 215.7 (C-11), 210.3 (C-8), 172.6 (C-2), 137.3 (C-7), 50.6 (C-1), 50.5 (C-9), 47.70 (C-10), 41.0 (C-12), 23.5 (Me at C-9), 26.6, 23.4, 22.2, 20.3 (C-3–C-6); MS 204; exact mass found 204.1143, $C_{13}H_{16}O_2$ requires 204.1150.

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-(cyclopent-1′-enyl)-cyclohexane (43) was prepared as described above for **3** from **6** (1.57 g, 4 mmol), **2** (0.5 g, 4.4 mmol), and BF_3 (500 mL, 20 mmol) as a mixture of cis and trans adducts **43a** and **43b** (1.87 g, 90% yield, R_f = 0.66 and 0.55, respectively, ether–hexane, 4:1, a:b = 2:1). A portion of this sample was separated into individual isomers by PTLC, and the latter were decomplexed for the spectral identifications.

43a (for the decomplexed sample): ^{1}H NMR 6.73 (1 H, m), 3.31 (3 H, s), 3.23 (1 H, dd, J = 10.2, 3.9 Hz), 2.56 (1 H, s), 2.2–2.6 (4 H, m), 2.28 (1 H, m), 1.9 (2 H, m), 1.2–1.8 (7 H, m); MS m/e 232. **43b** (for the decomplexed sample): ^{1}H NMR 6.73 (1 H, br s), 3.32 (3 H, s), 3.58 (1 H, t, J = 5.0 Hz), 2.52 (1 H, s), 2.2–2.6 (4 H, m), 2.28 (1 H, m), 1.9 (2 H, m), 1.2–1.8 (8 H, m); MS m/e 232.

Tetracyclo[10.3.0.0^{1,9}0^{3,8}]pentadeca-3(8),9-diene-2,11-dione (44). Cyclization of the mixture of **43a,b** (0.52 g, 1 mmol) was carried out on Florisil (Fluka 5.2 g) at 85 °C for 12 h, as was described for the preparation of **40–42**. After PTLC, **44** (0.121 g, yield 53%) was obtained as a colorless liquid (R_f = 0.45, EtOAc–hexane, 1:1): ^{1}H NMR 5.85 (1 H, s), 2.8 (1 H, d, J = 8.5 Hz), 2.5 and 2.25 (4 H, a pair of m), 1.6–2.0 (9 H, m), 1.3 (1 H, m); ^{13}C NMR 209.5 (C-11), 202.3 (C-2), 178.7 (C-9), 157.5 (C-8), 147.6 (C-3), 117.5 (C-10), 64.2 (C-1), 54.4 (C-12), 40.0, 30.3, 25.2, 24.0, 21.4 and 21.2 (C-13–C-15, C-4–C-7); IR 1705 (CO), 1611, 1594 cm^{-1} (C=C). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.07. Found: C, 78.69; H, 7.22. The structure was established by X-ray analysis. The same product **44** was formed in the trial experiments with individual **43a** and **43b**.

$Co_2(CO)_6$ complex of 1-methoxy-1-ethynyl-2-(cyclopent-1′-en-1′-yl]-cyclopentane 46 was prepared as described above for **3** from **28** (0.76 g, 2 mmol), 1-cyclopentenoyl fluoride (0.24 g, 2.1 mmol), and BF_3 (250 mL, 10 mmol) as a mixture of trans and cis adducts **46a** and **46b** (0.98 g, 97% yield, R_f = 0.64 and 0.52, respectively, ether–hexane, 4:1, a:b = 1:3). For the identification, a part of this sample was separated by PTLC into individual **46a** and **46b**, and the latter were oxidatively decomplexed into the respective metal-free acyl methoxy adducts.

46a (for the decomplexed sample): ^{1}H NMR 6.71 (1 H, br s), 3.29 (3 H, s), 3.35 (1 H, m), 2.53 (1 H, s), 2.1–2.5 (4 H, m), 1.2–2.0 (8 H, m); MS m/e 218. **46b** (for the decomplexed sample): ^{1}H NMR 6.74 (1 H, br s), 3.32 (3 H, s), 3.22 (1 H, m), 2.57 (1 H, s), 2.2–2.5 (4 H, m), 1.2–1.8 (8 H, m); MS m/e 218.

7-Methoxytetracyclo[9.3.0.0^{1,8}0^{3,7}]tetradec-8-ene-2,10-dione (47). The above mixture **46a,b** (1.01 g, 2 mmol) was dissolved in ether–pentane (20 mL, 1:1) and heated in a sealed vessel at 60 °C for 9 h. After removal of the solvent, the dark red residue was separated by PTLC into two major components, namely, **46b**, identical with material described above (0.66 g, 89% of the recovery for the initial convent of **46b**), and tetracyclic adduct **47** (0.09 g, yield 19% or ca. 70% for the content of **46a**) as colorless crystals: mp 63–65 °C (hexane); ^{1}H NMR 6.03 (1 H, s), 3.35 (3 H, s), 3.3 (1 H, m), 2.85 (1 H, m), 1.2–2.3 (12 H, m); the structure was established by X-ray analysis; MS m/e 246 (M^+); exact mass found M^+ 246.1250, $C_{15}H_{18}O_3$ requires 246.1256.

Recovered **46b** (0.66 g, 1.31 mmol) was dissolved in CH_2Cl_2 (13 mL), cooled down to −70 °C, and treated with gaseous BF_3 (165 mL, 6.5 mmol). The mixture was kept at this temperature for 20 min and then quenched with MeOH (absolute, 2 mL). After the usual treatment the mixture **46a,b** was isolated (0.56 g, yield ca. 85%, a:b = 3:1) and identified by ^1H NMR data comparison of the decomplexed material with the abovementioned sample.

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The Enantioselective Synthesis of (−)-Physostigmine via Chiral Sulfoxides

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Abstract: The total synthesis of naturally occurring (−)-physostigmine is described. The key element for the asymmetric induction is the chirality transfer from optically active 2-(alkylsulfinyl)indoles to indoline butyrolactones bearing two chiral centers. Novel features of this synthesis involve the use of a new class of sulfoxylating agents, *N*-(alkylsulfinyl)oxazolidinones, to prepare the starting indolyl sulfoxides and the correlation of the size of the alkyl group on the sulfoxide with the degree of asymmetric induction. The overall synthesis requires a dozen steps from commercially available 5-(benzyloxy)indole.

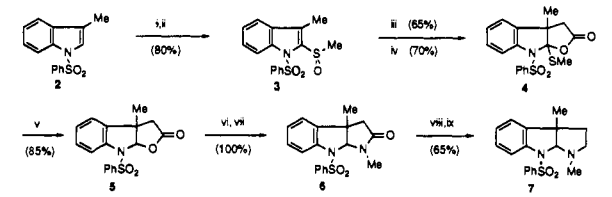
Introduction

A principal alkaloid of the Calabar bean, (−)-physostigmine (**1**), is a clinically useful anticholinesterase which has been used in the treatment of myasthenia gravis and glaucoma. More recently, analogues of (−)-physostigmine have also shown promise as therapeutic agents for Alzheimer's disease.[1,2] The importance of this class of alkaloids has elicited a large amount of synthetic work toward the total synthesis of the naturally occurring (−)-physostigmine. Earlier syntheses by and large produced only racemic physostigmine.[3] In recent years, a number of enantiocontrolled syntheses have been reported[4] for both the natural and unnatural physostigmine. Our interest in physostigmine emanated from the asymmetric synthesis of highly functionalized butyrolactones using chiral vinyl sulfoxides.

In a previous communication,[5] we showed that 2-(methylsulfinyl)indole **3** could serve as a unique precursor for the physostigmine alkaloids via lactonization with dichloroketene (Scheme I). Moreover, recent reports from our group[6] have established that the lactonization of chiral vinyl sulfoxides with dichloroketene occurs with complete control of the relative and absolute configuration.

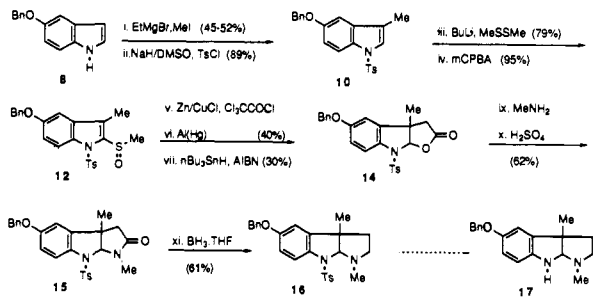
In this paper we want to summarize our earlier efforts toward racemic physostigmine and report a unique synthesis of optically active (−)-physostigmine, which involves the preparation of chiral indolyl sulfoxides and their use in the lactonization reaction.

Scheme I[a]

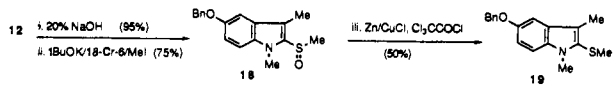


[a] Reagents: (i) 1.2 equiv of BuLi, THF, −23 °C. (ii) 5 equiv of MeSOCl, THF, −23 °C. (iii) 5 equiv of Cl_3CCOCl, 20 equiv of Zn-(Cu), THF, 0 °C. (iv) 20 equiv of Al(Hg), $THF/H_2O/MeOH$ (10/1/1), room temperature. (v) *n*-Bu_3SnH, AIBN, benzene, 80 °C. (vi) Excess $MeNH_2$, 10 equiv of 1 N HCl, anhydrous MeOH, −78 °C; cat. concentrated H_2SO_4, DMF, 115 °C. (viii) $Et_3O^+BF_4^-$, CH_2Cl_2, room temperature, $NaBH_4$, EtOH, 0 °C → room temperature.

Scheme II



Scheme III



Synthesis of Racemic Physostigmine

Reaction of 5-(benzyloxy)indole (**8**) with ethylmagnesium bromide and methyl iodide afforded 5-(benzyloxy)-3-methylindole. Treatment with dimsyl sodium and tosyl chloride effected sulfonylation at the nitrogen. Deprotonation at the C-2 carbon (BuLi, −60 °C), followed by addition of dimethyl disulfide, produced the 2-(methylsulfenyl)indole derivative of **10**. The racemic sulfoxide **12** was easily obtained by oxidation with *m*-CPBA (Scheme II). The lactonization protocol calls for treatment of the vinyl sulfoxide

(1) Davis, K. L.; Mohs, R. C. *Am. J. Psychiatry* **1982**, *139*, 1421. Beller, S. A.; Overall, J. E.; Swann, A. C. *Psychopharmacology* **1987**, *87*, 145.
(2) Christie, J. E.; Shering, A.; Ferguson, J.; Glen, A. I. *Br. J. Psychiatry* **1981**, *138*, 46.
(3) For a review of synthetic approaches to the physostigmines, see: Takano, S.; Ogasawara, K. *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 225-251.
(4) (a) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982-5984. (b) Node, M.; Hao, X.; Fuji, K. *Chem. Lett.* **1991**, 57-60. (c) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872-875. (d) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411-414. (e) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109-112. (f) Yu, Q.; Brossi, A. *Heterocycles* **1988**, *27*, 745-750. (g) Takano, S.; Goto, E.; Himara, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641-2643.
(5) Marino, J. P.; Kim, M.-W.; Lawrence, R. *J. Org. Chem.* **1989**, *54*, 1782-1784.
(6) (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643-7644. (b) Marino, J. P.; Fernandez de la Pradilla, R. *Tetrahedron Lett.* **1985**, *26*, 5382-5384. (c) Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *Synthesis* **1987**, 1088-1091. (d) Marino, J. P.; Laborde, E.; Paley, R. *J. Am. Chem. Soc.* **1988**, *110*, 966-968.

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