A Model Study towards a Conceptually New Synthetic Entry into the Seco- and Heteroyohimbine Alkaloid Families

by **Thomas Vogelsang**[1]) and **Hans-Jürg Borschberg***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH Hönggerberg, CH-8093 Zürich
(phone: 01 632 44 96; e-mail: borschberg@org.chem.ethz.ch)

Dedicated to Professor *Duilio Arigoni* on the occasion of his 75th birthday

A model study is presented that paves the way to a new and flexible synthetic approach towards the seco- and heteroyohimbine alkaloid class. The key step involves a highly diastereoselective *Cope* rearrangement of an (*E*,*E*)-azacyclodeca-3,7-diene grafted onto a 3-ethylindole moiety to furnish a *trans*-3,4-divinylpiperidine derivative in 83% yield.

1. Introduction. – The *Corynanthe* alkaloids, also known as secoyohimbine alkaloids, are represented by the general structure **A** (*Scheme 1*) (for reviews, see [2]). Together with the closely related heteroyohimbine class (general structure **B**), they represent early stages in the biosynthesis of the monoterpene indole alkaloids that are derived from secologanine[2]). Though *ca.* 400 representatives of class **A** and **B** have been isolated from various plants [2c], only in a very few cases have their pharmacological properties been investigated. On the other hand, some alkaloids belonging to the related *Yohimbine* family (Type **C**, *Scheme 1*) present interesting biological profiles, yohimbine itself, *e.g.*, shows antidiuretic and hypertensive activity. It is used clinically as antidepressant and to alleviate epileptic attacks. The isomeric α-yohimbine is a strong and selective α_2-adrenoceptor antagonist, whereas corynanthine shows a strong interaction with the corresponding α_1-adrenoceptor. Reserpine, venenantrine, and mitraphylline are hypotensive agents and show general-depressant activities.

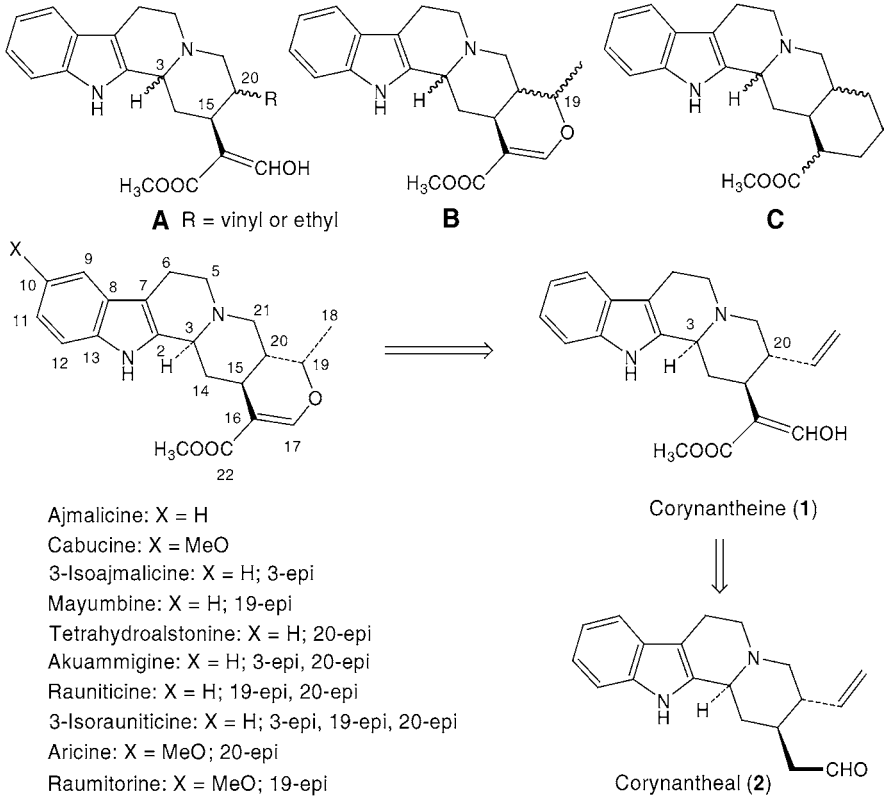
The structures of all representatives of the above indole alkaloid classes have one point in common: as a result of their biosynthesis, the absolute configuration at C(15) is invariably (*S*). In contrast, the configuration at the remaining chiral centers (3, 19, and 20) is variable, and, in fact, all possible combinations have been detected in the natural products. Whereas many synthetic approaches to individual members in this series have been published [2], there is no strategy available that is flexible enough to provide access to all possible diastereoisomers by taking recourse to only minor tactical manoeuvres. In addition, it would be helpful if the indole unit was introduced in a late

---

[1]) Taken from the PhD thesis of *T. V.* [1].

[2]) Presently, only four classes of monoterpenoid indole alkaloids that are derived by combination of an intact C_{10} precursor with tryptamine are known: the *Aristotelia* and the *Borreria* alkaloids, both occurring in plants, besides the hapalindoles and the teleocidines, produced *inter alia* by terrestrial blue-green algae (for a review, see [3]).

Scheme 1

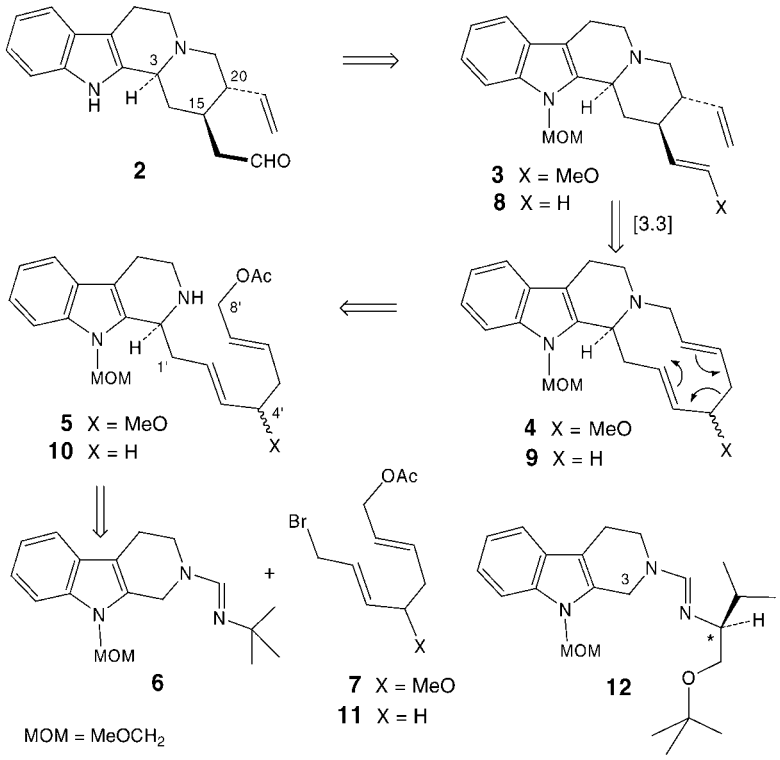


stage of the synthesis to gain ready access to representatives endowed with MeO groups at various positions of the benzene ring.

2. Retrosynthesis. – In the above context, we considered the following retrosynthetic scheme as potentially useful (*Schemes 1* and *2*) (for a preliminary account, see [4]). The alkaloids containing a C_{20} skeleton like corynantheine (**1**) are readily available from the 22-nor compounds like corynantheal (**2**), usually through formylation of the corresponding ester [2c]. The enol ether equivalent to **2** represents a substituted 3,4-divinylpiperidine derivative, like **3**. In general, such 1,2-divinylcycloalkanes are related to medium-ring sized cycloalka-1,5-dienes *via* a *Cope* rearrangement process (for reviews, see [5]). Generally, this type of sigmatropic inter-relation is represented by an equilibrium whose position depends critically upon the respective ring sizes present in the two components as well as on their substitution patterns. As illustrated in *Table 1*, the presence of strained three- or four-membered rings at the expense of seven- or eight-membered rings shifts the equilibrium completely towards the ring-expanded side (*Entries 1* and *2*). At the same time, the activation energy for the rearrangement of *cis*-1,2-divinylcyclopropane amounts to only 19.4 kcal/mol [6], as

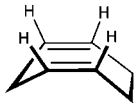
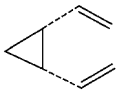
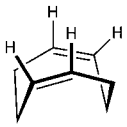
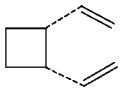
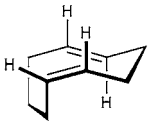
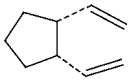
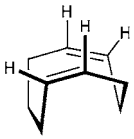
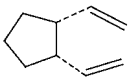
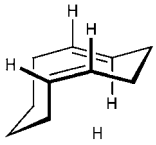
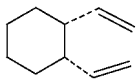
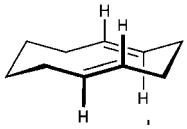
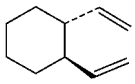
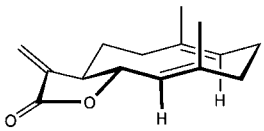
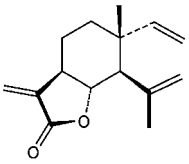
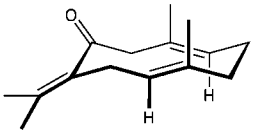
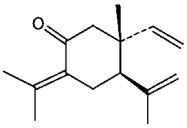
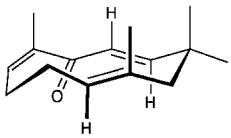
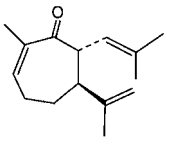
compared to 33.5 kcal/mol determined for the standard hexa-1,5-diene [7]. For *cis*-1,2-divinylcyclobutane, an intermediate value of 23.1 kcal/mol was reported [8]. This situation changes dramatically when the involved ring perimeters become larger, in that the ring-contracted compound now becomes the dominant component in the *Cope* equilibrium [9–15] (see *Table 1*, *Entries 3–11*).

Scheme 2



The report that in the case of cyclodeca-1,5-diene, the equilibrium lies completely on the 1,2-divinylcyclohexane side and that the stereochemical outcome is determined by the configuration of the starting C=C bonds (*Entries 5* and *6*) [11][12] prompted us to devise the retrosynthesis displayed in *Scheme 2*. Enol ether **3** should result from the *Cope* rearrangement of the azacyclodeca-3,7-diene precursor **4**. The latter can be traced back to a ring-open precursor, such as **5**, which should be easy to prepare by application of the well-established protocol of *Meyers* and *Loewe* [16], which consists of α-metallation of mixed formamidines (= formimidamides), followed by an alkylation with the appropriate electrophile. In our case, the readily prepared formamidine **6** should be alkylated with the allyl bromide **7**. An attractive feature of the chosen approach is the finding of *Meyers*'s group that excellent asymmetric induction in the alkylation step can be expected in the presence of a chiral auxiliary within the formamidine function. A case at hand is the valinol-derived chiral amidine **12** [17].

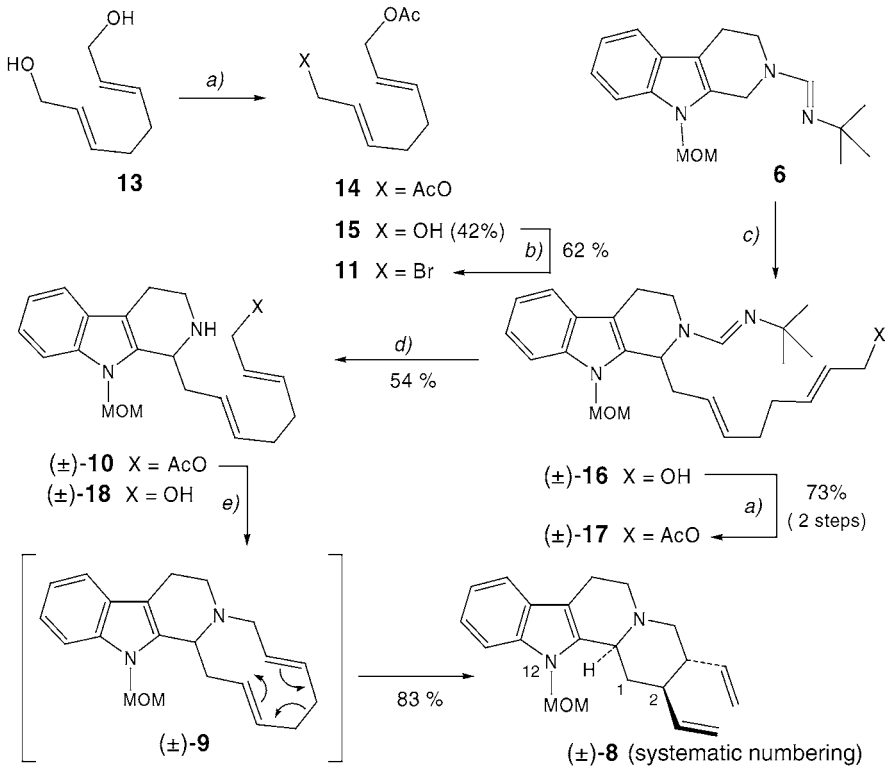
Table 1. Cope *Rearrangements of Medium-Ring 1,5-Dienes*

Entry	Configuration	Cycloalka-1,5-diene	Reaction conditions and transition state	Divinylcycloalkane	Ref.
1	(*Z*,*Z*)		– 20° boat / *cis*		[6]
2	(*Z*,*Z*)		80° boat / *cis*		[8]
3	(*Z*,*E*)		130° chair / *cis*		[9]
4	(*Z*,*Z*)		220° 5 : 95 boat / *cis*		[10]
5	(*Z*,*E*)		150° chair / *cis*	 100%	[11]
6	(*E*,*E*)		70° chair / *trans*	 100%	[12]
7	(*E*,*E*)		230° 1 : 2 chair / *trans*		[13]
8	(*E*,*E*)		165° chair / *trans*		[14]
9	(*E*,*E*)		160° chair / *trans*		[15]

As the stereochemical outcome of the *Cope* reaction, depicted as shown in formulae **2** and **3**, was at best the result of wishful thinking, we decided to simplify matters and to start our investigation with the simpler demethoxy system **8**–**10**, beginning with the bromo acetate **11** as the alkylating agent.

3. Results and Discussion. – The required bromo acetate **11** was prepared from the readily available (*E*,*E*)-dienediol **13** [18], which on treatment with 1 equiv. of acetyl chloride gave in 42% yield the desired monoacetate **15** besides unreacted starting material and some diacetate **14**, which can be recycled (*Scheme 3*). Treatment of **15** with PBr_3 furnished the required building block in which both C=C bonds still had the (*E*)-configuration. Metallation of the indole-protected amidine **6**, readily accessible from 1,2,3,4-tetrahydro-β-carboline (=2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole) [19], followed by alkylation with **11**, furnished a mixture of (±)-**17** and (±)-**16**, which was re-acetylated to give (±)-**17** in 73% combined yield. The removal of the formamidine group under the standard conditions by using hydrazine hydrate as a reagent furnished amino alcohol (±)-**18**. On the other hand, we found that treatment of

Scheme 3



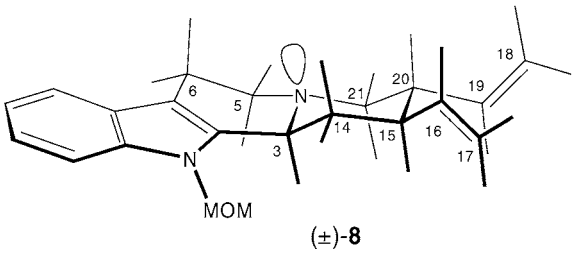
a) AcCl, Et_3N, CH_2Cl_2, 0°, 30 min. *b*) PBr_3, Et_2O, 0°, 90 min. *c*) *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine, ^{t}BuLi, THF, **11**, −70°, 30 min. *d*) N_2H_4, THF, AcOH, 60°, 5 h. *e*) [Pd(PPh_3)$_4$], PPh_3, 1,2,2,6,6-pentamethylpiperidine, THF, 50°, 20 h.

(±)-**17** with a commercially available 1M anhydrous hydrazine solution in THF in the presence of AcOH furnished chemoselectively amino acetate (±)-**10**.

After the more-classical attempts to effect the ensuing intramolecular amino-alkylation of (±)-**18** and related, more-reactive derivatives to give (±)-**9** had all failed, we resorted to *Trost*'s methodology, which uses Pd^0 catalysts to promote nucleophilic attack of amines at allylic acetates (for a review, see [20]). Indeed, treatment of (±)-**10** with [$Pd(PPh)_4$] and 1,2,2,6,6-pentamethylpiperidine in refluxing THF for 20 h furnished essentially a single product in 83% yield. A glance at the NMR spectra of this material showed that it did not possess the expected structural formula (±)-**9**. In accord with the detailed spectral analysis, structure (±)-**8** was assigned to the isolated product, resulting from a *Cope* rearrangement of the putative intermediate (±)-**9**.

The MS of (±)-**8** displayed an M^+ at *m/z* 322 ($C_{21}H_{26}N_2O^+$), indicating the expected formal loss of AcOH from the starting (±)-**10**. The presence of two vinyl groups at the expense of the two formerly 1,2-disubstituted (*E*)-double bonds was readily apparent in the ^{13}C-NMR spectrum, in that two new *t* could be discerned at δ 116.0 and 114.4, which are correlated *via* HETCOR with a complex signal at δ 5.0 (4 H). The two remaining olefinic protons show up at δ 5.72 (*ddd, J* = 17.2, 10.4, 7.5 Hz) and 5.63 (*ddd, J* = 17.2, 10.4, 8.1 Hz), which correlate with 2 *d* at δ 141.2 and 139.7, respectively. Judging from the respective chemical shifts, the aliphatic N-atom is connected to a CH and two CH_2 groups (δ 56.9(*d*)/3.81; δ 60.6 (*t*)/3.10 and 2.72; δ 48.6 (*t*)/3.19 and 2.75). The remaining signals are readily accounted for by the constitutional formula **8**. The relative configuration at the three asymmetric centers of (±)-**8** was deduced as follows: the presence of a distinct *Bohlmann* band at 2755 cm^{-1} in the IR spectrum points to the presence of a *trans*-quinolizidine system [21]. The pseudoaxial nature of H–C(3) also follows from the observed vicinal coupling constant with H_{ax}–C(14) (11.4 Hz) (for numbering, see the *Fig.*). The equatorial orientation of both vinyl groups could be determined by analyzing the coupling patterns in their neighborhood (see the *Fig.*). For this purpose, we had to take recourse to a ^{1}H-NMR spectrum (500 MHz) recorded in C_6D_6 which was better resolved and mostly first-order.

The ease with which the above reaction proceeds is in accordance with a precedent case (*Table 1*, *Entry 6*), but an acceleration of the *Cope* rearrangement by traces of Pd^{II} which is known to catalyze [3,3] processes [22] can presently not be excluded. The finding that only one diastereoisomer (*normal*-type, see *Scheme 4*) is formed is somewhat surprising if one considers the conformational flexibility of the putative precursor (±)-**9**. Conformers that would lead to the isomeric *pseudo*-, *allo*-, and *epiallo*-skeletons are certainly available and in equilibrium with the conformers that lead to the single product (±)-**8**. In fact, semi-empirical calculations of the corresponding local minima showed that they differ not too much in their heats of formation, and the same

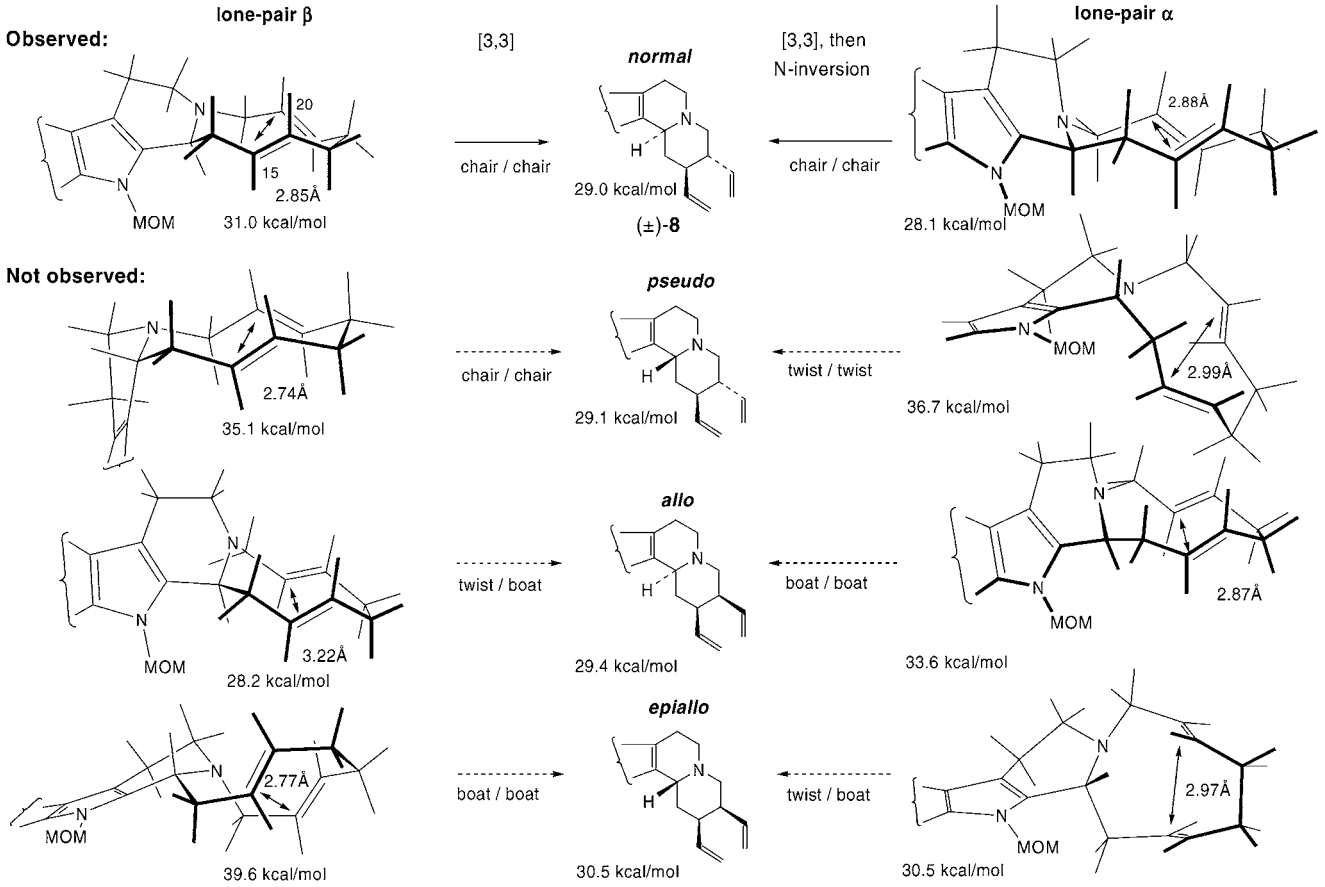


(±)-**8**

Dihedral angles	τ	^3J [Hz]
H–C(3) / H_{ax}–C(14)	179°	11.3
H–C(3) / H_{eq}–C(14)	62°	2.7
H_{ax}–C(14) / *H*–C(15)	175°	12.0
H_{eq}–C(14) / *H*–C(15)	59°	4.0
H–C(15) / *H*–C(20)	175°	*ca.* 11
H–C(20) / H_{ax}–C(21)	173°	11.2
H–C(20) / H_{eq}–C(21)	56°	4.0

Figure. *Geometry and pertinent dihedral angles of (±)-***8** *as calculated by PM3 and observed vicinal coupling constants* (^{1}H-NMR, 500 MHz, C_6D_6). Unlabelled substituents represent H-atoms. Trivial numbering.

Scheme 4. *Some Local Minima of the Intermediate (±)-***9** *as Calculated by PM3* (ΔH_f° in kcal/mol). Unlabelled substituents represent H-atoms. The first stereochemical descriptor refers to the initial conformation of the formed piperidine ring and encompasses atoms 1–3 and 8–10 of the (*E*,*E*)-azacyclodeca-3,7-diene system, the second refers to the conformation of the transition state of the *Cope* rearrangement, encompassing the centers 3–8.



is true for the possible products, the four diastereoisomeric divinylpiperidines (*Scheme 4*). In acyclic cases, the *Cope* reaction is known to proceed *via* a chair-type transition state, which is favored by *ca.* 8 kcal/mol over the boat-type alternative [5] [23]. In our case, a chair-type transition state can readily be taken up geometrically and should be favored by about the same amount as in the acyclic cases. This factor strongly disfavors the pathways that would lead to the *allo*- and *epiallo*-isomers. The pathways leading to the *normal*- and the *pseudo*-type skeletons differ in that, in the former case, a *trans*-quinolizine system is formed, which is expected to be substantially more stable than its *cis*-counterpart, formed along the latter pathway[3]). Obviously, this difference in favor of the *normal*-type isomer manifests itself already in the preceding respective transition states.

4. Conclusions. – The success of the described model study bodes well for a future stereoselective elaboration of *Corynanthe*- and heteroyohimbine alkaloids. It will also be of interest to investigate the stereochemical outcome of the *Cope* rearrangement, when the geometrical double bond isomers of **7** and **11** are employed as precursors.

We express our gratitude to the former *Stipendienfonds der Basler Chemischen Industrie* for generous financial support (*T. V.*). We also thank our former chemical technician apprentice, Mr. *R. Scherrer,* for his extensive experimental contributions to the presented and related projects.

Experimental Part

General. See [25]. CC = Column chromatography. For assignments of the ^{13}C-NMR spectra, see *Table 2*.

*(2*E*,6*E*)-8-Hydroxyocta-2,6-dienyl Acetate* (**15**). To a soln. of **13** (4.75 g, 33.4 mmol) [18] and Et_3N (4.5 ml, 32 mmol; *Fluka, puriss.*) in CH_2Cl_2 (250 ml) was added dropwise AcCl (2.13 ml; 30 mmol; *Fluka*, *puriss.*) at 0°. After stirring at 0° for 30 min, the mixture was poured into sat. aq. NH_4Cl soln. (200 ml). The aq. phase was extracted 3 times with AcOEt, the combined org. layer dried ($MgSO_4$) and evaporated, and the crude material (8.2 g) purified by CC (silica gel, pentane/AcOEt/EtOH 9 : 1 : 0 → 2 : 1 : 0 → 6 : 3 : 1): 2.14 g (28%) of **14**, 2.64 g (42.9%) of **15**, and 1.44 g (30%) of **13**.

Data of **15**: Colorless oil. IR ($CHCl_3$): 3620, 3470 (br.), 3015, 2950, 1735, 1676, 1452, 1388, 1370, 1090, 1030, 975, 913, 665. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.76-5.53 (*m*, 4 H); 4.48 (*m*, 2 H); 4.06 (*m*, 2 H); 2.13 (*m*, 4 H); 2.03 (*s*, 3 H); 1.75 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.2 (*s*); 135.7 (*d*); 132.0 (*d*); 130.0 (*d*); 124.7 (*d*); 65.2 (*t*); 63.7 (*t*); 31.8 (*t*); 31.5 (*t*); 21.0 (*q*). EI-MS: 124 (1, $[M-60\,(AcOH)]^+$), 106 (6), 70 (39), 54 (44), 43 (100), 41 (24), 39 (19), 27 (15).

*(2*E*,6*E*)-8-Bromoocta-2,6-dienyl Acetate* (**11**). To a soln. of **15** (2.638 g, 14.3 mmol) in Et_2O (100 ml) was added slowly PBr_3 (0.94 ml, 10 mmol; *Fluka*, *purum*) at 0°. After stirring at 0° for 90 min, the mixture was worked up with sat. aq. $NaHCO_3$ soln. The combined org. layer was dried ($MgSO_4$) and evaporated, and the residue dried for 4 h at 23°/0.01 Torr: 2.2 g (62%) of pure **11**. Colorless oil. IR ($CHCl_3$): 3020, 2940, 2850, 1735, 1662, 1438, 1384, 1362, 1110, 1080,1025, 969. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.9–5.5 (*m*, 4 H); 4.50 (*d, J* = 6.2, 2 H); 3.93 (*d, J* = 6.5, 2 H); 2.16 (*m*, 4 H); 2.05 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.1 (*s*); 135.5 (*d*); 135.1 (*d*); 127.3 (*d*); 125.0 (*d*); 65.1 (*t*); 33.2 (*t*); 31.5 (*t*); 31.3 (*t*); 21.0 (*q*). EI-MS: 205 and 203 (0.3, $[M-43]^+$), 167 (3), 107 (21), 79 (18), 54 (23), 52 (20), 43 (100), 41 (16), 39 (20), 27 (12).

*(2*E*,6*E*)-8-{2-{[(1,1-Dimethylethyl)imino]methyl}-2,3,4,9-tetrahydro-9-(methoxymethyl)-1*H*-pyrido[3,4-b]indol-1-yl}octa-2,6-dienyl Acetate* ((±)-**17**). *Method A*. To a soln. of **6** [19] (2.35 g, 7.8 mmol) and *N,N,N′,N′*-tetramethylethane-1,2-diamine (1.5 ml; 10 mmol; *Fluka*, *puriss.*) in THF (50 ml) was added 1.5M ^{t}BuLi in

---

[3]) The parent system *cis*-quinolizidine was shown to be destabilized by 2.6 kcal/mol compared to its *trans*-counterpart [24] (*cis*/*trans* refer to the position of H–C(9a) with respect to the lone electron pair at N(4)). In the present case, this difference in stability should be even greater due to an additional unfavorable interaction between *H*–C(15) and the $MeOCH_2$ protecting group.

Table 2. *^{13}C-NMR Chemical-Shift Values* δ [ppm]. In $CDCl_3$ at 23°.

	6	**11**	**13**	**15**	(±)-**16**	(±)-**17**	(±)-**18**	(±)-**10**	(±)-**8**[a])
C(2)	132.3				135.9	136.0	136.7	137.0	136.6
C(3)	45.7				52.1[c])	51.7[c])	50.6	50.8	56.9
C(5)	41.2				39.5[c])	39.6[c])	38.6	39.0	48.6
C(6)	21.8				21.1	21.1	22.4	22.6	22.2
C(7)	109.4				109.7	109.7	110.4	110.4	110.3
C(8)	127.4				127.3	127.4	127.5	127.6	127.3
C(9)	118.0				118.3	118.2	118.2	118.2	118.3
C(10)	120.0				120.0	120.0	119.9	119.9	119.9
C(11)	121.8				122.1	122.0	121.9	121.9	121.8
C(12)	109.4				109.5	109.5	109.3	109.3	109.3
C(13)	137.3				137.6	137.6	137.5	137.5	138.2
C(1′)		33.2	63.7	63.7	37.6	37.4	37.0	37.1	
C(2′)		135.1	132.4	132.0	131.7	131.9	133.5	133.0	
C(3′)		127.3	129.9	130.0	127.0	127.3	127.6	127.3	
C(4′)[b])		31.3	31.7	31.8	32.0	32.0	32.1	32.2	
C(5′)[b])		31.5	31.7	31.5	31.9	32.1	31.9	31.9	
C(6′)		125.0	129.9	124.7	130.1	124.2	130.2	124.3	
C(7′)		135.5	132.4	135.7	132.5	135.7	132.3	135.6	
C(8′)		65.1	63.7	65.4	63.4	65.2	63.6	65.2	
MeO*C*H$_2$ (*t*)	74.1				74.3	74.3	74.2	74.3	74.5
*Me*OCH$_2$ (*q*)	55.8				55.9	55.9	55.8	55.8	55.7
CH=N (amidine; *d*)	150.3				150.6	149.9			
Me$_3$*C* (amidine; *s*)	53.3				53.2	53.0			
Me$_3$C (amidine; *q*)	31.3				31.2	31.2			

[a]) Assignments corroborated by HETCOR experiments. [b]) Assignments may be interchanged. [c]) Broad signals under the given recording conditions.

hexane (6 ml, 9 mmol; *Fluka*, *techn.*) at −78°. After stirring for 10 min at −78°, a soln of **11** (2.0711 g, 8.38 mmol) in THF (20 ml) was added to the dark soln. After stirring for 30 min, MeOH (2 ml) was added, and the resulting mixture was evaporated. Workup with CH_2Cl_2/sat. aq. Na_2CO_3 soln. furnished 4.5 g of crude material, which was separated by CC (silica gel, cyclohexane/ ^{t}BuOMe/EtOH 4:1:0 → 6:4:1, always with 5% of Et_3N): 500.1 mg (14%) of less-polar (±)-**17** and 2.158 g (65%) of more-polar (±)-**16**.

*Data of (±)-***17**: Colorless viscous oil. IR ($CHCl_3$): 3005, 2970, 2930, 2845, 1737, 1641, 1465, 1419, 1383, 1362, 1339, 1308, 1240, 1109, 1062, 1028, 970, 930, 670, 665. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (*dm, J* = 7.7, 1 H); 7.43 (*s*, 1 H); 7.41 (*dm, J* = 8.4, 1 H); 7.26-7.14 (*m*, 2 H); 5.76 (*m,* 1 H); 5.61-5.48 (*m*, 3 H); 5.48 (*d, J* = 11.2, 1 H); 5.34 (*d, J* = 11.2, 1 H); 5.12 (br. *m*, 1 H); 4.50 (*dd, J* = 6.4, 0.8, 2 H); 4.04 (br. *s*, 1 H); 3.40 (br. *m*, 1 H); 3.28 (*s*, 3 H): 2.84 (br. *dddd, J* = 11.5, 10.5, 6.0, 4.9, 1 H); 2.71–2.62 (*m*, 2 H); 2.58–2.51 (*m*, 1 H); 2.17–2.10 (*m*, 4 H); 2.05 (*s*, 3 H), 1.14 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.8 (*s*); 149.9 (*d*); 137.6 (*s*); 136.0 (*s*); 135.7 (*d*); 131.9 (*d*); 127.4 (*s*); 127.3 (*d*); 124.2 (*d*); 122.0 (*d*); 120.0 (*d*); 118.2 (*d*); 109.7 (*s*); 109.5 (*d*); 74.3 (*t*); 65.2 (*t*); 55.9 (*q*); 53.0 (*s*); 51.7 (br. *d*); 39.6 (br. *t*); 37.4 (*t*); 32.1 (*t*); 32.0 (*t*); 31.2 (3 *q*); 21.1 (*t*); 21.0 (*q*). FAB-MS: 466 (100), 465 (15, M^+), 464 (20), 351 (11), 299 (15), 298 (28), 242 (10), 215 (50), 213 (15).

*Data of (±)-***16**: Colorless viscous oil. IR ($CHCl_3$): 3615, 3540 (br.), 3005, 2970, 2930, 2845, 1740, 1466, 1361, 1340, 1308, 1240, 1185, 1109, 1082, 1062, 971, 910. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (*dm, J* = 7.7, 1 H); 7.44 (*s*, 1 H); 7.41 (*dm, J* = 8.2, 1 H); 7.26–7.14 (*m*, 2 H); 5.62 (*m,* 2 H); 5.46 (*m*, 3 H); 5.35 (*d, J* = 11.1, 1 H); 5.04 (br. *s*, 1 H); 4.07 (*m*, 2 H); 3.38 (br. *s*, 1 H); 3.29 (*s*, 3 H): 2.87 (*m*, 1 H); 2.71–2.62 (*m*, 2 H); 2.58–2.50 (*m*, 1 H); 2.17–2.10 (*m*, 4 H); 1.15 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 150.6 (*d*); 137.6 (*s*); 135.9 (*s*); 132.5 (*d*); 131.7 (*d*); 130.1 (*s*); 127.3 (*d*); 127.0 (*d*); 122.1 (*d*); 120.0 (*d*); 118.3 (*d*); 109.7 (*s*); 109.5 (*d*); 74.3 (*t*); 63.4 (*t*); 55.9 (*q*); 53.2 (*s*); 52.1 (br. *d*); 39.6 (br. *t*); 37.6 (*t*); 32.0 (*t*); 31.9 (*t*); 31.2 (3 *q*); 21.1 (*t*). FAB-MS: 424 (100), 423 (11, M^+), 422 (16), 299 (21), 298 (34), 242 (16), 215 (70), 213 (21).

Method B. To a soln. of (±)-**16** (2.071 g, 4.89 mmol) in CH_2Cl_2 (200 ml) were added Et_3N (0.7 ml, 5 mmol) and AcCl (0.355 ml, 5 mmol) at 0°. After stirring for 30 min, the mixture was worked up with CH_2Cl_2/sat. aq. Na_2CO_3 soln.: 2.20 g (96.6%) of pure (±)-**17**. Combined yield of (±)-**17** after application of *Methods A* and *B:* 2.70 g (74.3%).

*(2*E*,6*E*)-8-[2,3,4,9-Tetrahydro-9-(methoxymethyl)-1*H*-pyrido[3,4-*b*]indol-1-yl]octa-2,6-dienyl Acetate* ((±)-**10**). To a soln. of (±)-**17** (303 mg, 0.65 mmol) in THF (20 ml) were added AcOH (0.37 ml, 6.5 mmol) and 1M anh. N_2H_4 in THF (6.5 ml; *Fluka*) at 0° under Ar. The mixture was stirred at 60° for 5 h, cooled to 0°, and worked up with CH_2Cl_2/aq. Na_2CO_3 soln. The crude product was purified by FC (silica gel, cyclohexane/^{t}BuOMe/Et_3N 76:19:5): 135 mg (54%) of (±)-**10**. Colorless viscous oil. IR ($CHCl_3$): 3005, 2935, 2845, 1732, 1464, 1450, 1381, 1365, 1337, 1308, 1240, 1181, 1129, 1107, 1062, 1026, 995, 971, 910, 661. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (*ddd, J* = 7.7, 1.2, 0.7, 1 H); 7.41 (*dt, J* = 8.1, 0.8, 1 H); 7.21 (*ddd, J* = 8.1, 7.1, 1.3, 1 H); 7.13 (*ddd, J* = 7.7, 7.1, 1.0, 1 H); 5.76 (*dm, J* = 15.4, 1 H); 5.61–5.46 (*m*, 3 H); 5.42 (*d, J* = 11.1, 1 H); 5.34 (*d, J* = 11.1, 1 H); 4.50 (*dd, J* = 6.4, 0.8, 2 H); 4.14 (*t, J* = 6.2, 1 H); 3.26 (*s*, 3 H): 3.22 (*ddd, J* = 13.1, 8.4, 4.9, 1 H); 3.06 (*ddd, J* = 12.8, 5.4, 4.2, 1 H); 2.77 (*dddd, J* = 15.2, 8.4, 5.5, 1.4, 1 H); 2.69 (*dtm, J* = 15.2, 4.6, 1 H); 2.57 (*t, J* = 6.2, 2 H); 2.17–2.14 (*m*, 4 H); 2.06 (*s*, 3 H); 1.93 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.9 (*s*); 137.5 (*s*); 137.0 (*s*); 135.6 (*d*); 133.0 (*d*); 127.6 (*s*); 127.3 (*d*); 124.3 (*d*); 121.9 (*d*); 119.9 (*d*); 118.2 (*d*); 110.4 (*s*); 109.3 (*d*); 74.3 (*t*); 65.2 (*t*); 55.8 (*q*); 50.8 (*d*); 39.0 (*t*); 37.1 (*t*); 32.2 (*t*); 31.9 (*t*); 22.6 (*t*); 21.0 (*q*). FAB-MS: 383 (66), 382 (13, M^+), 381 (38), 351 (19), 216 (25), 215 (100), 213 (24), 183 (14), 171 (11), 169 (12).

*(2*RS*,3*RS*,5*RS*,12b*SR*)-2,3-Diethenyl-1,2,3,4,6,7,12,12*b*-octahydro-12-(methoxymethyl)indolo[2,3-α]quinolizine* ((±)-**8**). Note: 'degassed' means that Ar was bubbled through the soln. for 15 min through a syringe needle. To a degassed soln. of [Pd(PPh_3)$_4$] (40.4 mg, 0.035 mmol; *Fluka*, *purum*) and PPh_3 (92 mg, 0.35 mmol; *Fluka*, *purum*) in dry THF (40 ml) was added a degassed soln. of (±)-**10** (130 mg, 0.34 mmol) in THF (10 ml) at 23°. Then was added 1,2,2,6,6-pentamethylpiperidine (75 µl, 0.4 mmol; *Fluka*, *purum*), and the mixture was stirred at 23° for 30 min and then at 50° for 20 h. The solvent was distilled off at 50 Torr and the residue dissolved in CH_2Cl_2 (10 ml). After addition of silica gel (3 g), the solvent was evaporated and the residue transferred onto a column for CC (silica gel (17 g), packed with cyclohexane/AcOEt/Et_3N 76:19:5, eluted with the same solvent mixture): 91.4 mg (83.4%) of (±)-**8**. Slightly yellow oil. IR ($CHCl_3$): 3080, 3003, 2920, 2820, 2755, 1641, 1462, 1443, 1420, 1362, 1342, 1308, 1185, 1105, 1064, 1028, 995, 971, 918, 660. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.47 (*ddd, J* = 7.8, 1.1, 0.8, 1 H); 7.39 (*dm, J* = 8.2, 1 H); 7.19 (*ddd, J* = 8.2, 7.1, 1.2, 1 H); 7.12 (*ddd, J* = 7.8, 7.1, 1.0, 1 H); 5.72 (*ddd, J* = 17.2, 10.4, 7.5, 1 H); 5.63 (*ddd, J* = 17.2, 10.4, 8.1, 1 H); 5.42 (*d, J* = 11.2, 1 H); 5.37 (*d, J* = 11.2, 1 H); 5.10–4.99 (*m*, 4 H); 3.81 (br. *d, J* = 11.5, 1 H); 3.22 (*s*, 3 H): 3.19 (*m*, 1 H); 3.10 (*dd, J* = 12.7, 4.2, 1 H); 2.90 (*m*, 1 H); 2.85 (*m*, 1 H); 2.75 (*m*, 1 H); 2.72 (*dd, J* = 12.7, 11.4, 1 H); 2.31 (*m*, 1 H); 2.20 (*ddd, J* = 12.9, 3.9, 2.6, 1 H); 2.17 (*m*, 1 H); 1.64 (*qd, J* = 11.4, 1.5, 1 H). ^{1}H-NMR (500 MHz, C_6D_6): 7.58 (*m*, 1 H); 7.29–7.22 (*m,* 3 H); 5.70 (*ddd, J* = 17.2, 10.4, 7.5, 1 H); 5.63 (*ddd, J* = 17.2, 10.4, 8.1, 1 H); 5.06–4.98 (*m*, 4 H); 4.94 (*s*, 2 H); 3.61 (br. *dd, J* = 11.3, 2.1, 1 H); 2.99 (*dd, J* = 12.3, 4.2, 1 H); 2.94–2.85 (*m*, 2 H); 2.84 (*s*, 3 H): 2.70 (*m*, 1 H); 2.54 (*m*, 1 H); 2.53 (*dd, J* = 12.3, 11.2, 1 H); 2.28 (*ddd, J* = 13.3, 3.9, 2.5, 1 H); 2.24 (*m*, 1 H); 1.96 (*m*, 1 H); 1.65 (*dt, J* = 13.2, 11.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 141.2 (*d*); 139.7 (*d*); 138.2 (*s*); 136.6 (*s*); 127.3 (*s*); 121.8 (*d*); 119.9 (*d*); 118.3 (*d*); 116.0 (*t*); 114.4 (*t*); 110.3 (*s*); 109.3 (*d*); 74.5 (*t*); 60.6 (*t*); 56.9 (*d*); 55.7 (*q*); 48.6 (*t*); 45.6 (*d*); 42.8 (*d*); 33.7 (*t*); 22.2 (*t*). HETCOR (500/125 MHz, $CDCl_3$): 141.2/5.72; 139.7/5.63; 121.8/7.19; 119.9/7.12; 118.3/7.47; 116.0/5.08; 114.4/5.00; 109.3/7.39; 74.5/5.42 and 5.37; 60.6/3.10 and 2.72; 56.9/3.81; 55.7/3.22; 48.6/3.19 and 2.75; 45.6/2.17; 42.8/2.31; 33.7/2.20 and 1.64; 22.6/2.90 and 2.85. EI-MS: 322 (32, M^+), 321 (25), 291 (13), 281 (19), 277 (14), 267 (13), 228 (90), 215 (18), 214 (100), 213 (17), 183 (29), 169 (45), 168 (21), 140 (22).

REFERENCES

[1] T. Vogelsang, Dissertation Nr. 13647, ETH Zürich, 2000.

[2] a) W. A. Creasey, in 'The Monoterpenoid Indole Alkaloids', Ed. J. E. Saxton, John Wiley & Sons, Chichester, 1983, Vol. 4, p. 783; b) C. Szántai , G. Blaskó, K. Honty, G. Dörnyei, 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, Vol. 27, 1986, p. 131; c) M. Lounasmaa, A. Tolvanen, in 'The Monoterpenoid Indole Alkaloids', Supplement to Vol. 25, Part 4, Ed. J. E. Saxton, John Wiley & Sons, Chichester, 1994, Chapt. 3, p. 57.

[3] H.-J. Borschberg, in 'The Monoterpenoid Indole Alkaloids', Supplement to Vol. 25, Part 4, Ed. J. E. Saxton, John Wiley & Sons, Chichester, 1994, Chapt. 2, p. 15.

[4] C. Frauenfelder, G. A. Schmid, T. Vogelsang, H.-J. Borschberg, *Chimia* **2001**, *55,* 828.

[5] S. J. Rhoads, N. R. Raulins, *Org. React.* **1975**, 1; M. B. Smith, 'Organic Synthesis', McGraw-Hill, Inc., Singapore, 1994, Chapt. 11, p. 1233.

[6] J. M. Brown, B. T. Golding, J. J. Stofko Jr., *J. Chem. Soc., Chem. Commun.* **1973**, 319.
[7] W. von E. Doering, V. G. Toscano, G. H. Beasley, *Tetrahedron* **1971**, *27*, 5299.
[8] G. S. Hammond, C. D. DeBoer, *J. Am. Chem. Soc.* **1964**, *86*, 899.
[9] E. Vogel, W. Grimme, E. Dinné, *Angew. Chem., Int. Ed.* **1963**, *2*, 739.
[10] E. Vogel, H. Günther, *Angew. Chem., Int. Ed.* **1967**, *6*, 385.
[11] P. Heimbach, *Angew. Chem., Int. Ed.* **1964**, *3*, 702.
[12] C. A. Grob, H. Link, P. W. Schiess, *Helv. Chim. Acta* **1963**, *46*, 483.
[13] T. C. Jain, C. M. Banks, J. E. McCloskey, *Tetrahedron Lett*. **1970**, 841.
[14] G. Ohloff, E. G. Hoffmann, *Z. Naturforsch.*, *B.* **1961**, *16*, 298.
[15] H. N. Subba Rao, N. P. Damodaran, S. Dev, *Tetrahedron Lett*. **1967**, 227.
[16] A. I. Meyers, M. F. Loewe, *Tetrahedron Lett*. **1984**, *25*, 2641.
[17] A. I. Meyers, T. Sohda, M. F. Loewe, *J. Org. Chem.* **1986**, *51*, 3108; A. I. Meyers, T. K. Highsmith, P. T. Buonora, *J. Org. Chem.* **1991**, *56*, 2960; A. I. Meyers, *Aldrichim. Acta* **1985**, *18*, 59.
[18] E. Vedejs, M. J. Arnost, J. P. Hagen, *J. Org. Chem.* **1979**, *44*, 3230.
[19] A. I. Meyers, S. Hellring, *J. Org. Chem*. **1982**, *47*, 2229.
[20] B. M. Trost, *Angew. Chem*. **1989**, *101*, 1199.
[21] F. Bohlmann, *Chem. Ber*. **1958**, *91*, 2157.
[22] L. E. Overman, *Angew. Chem., Int. Ed.* **1984**, *23*, 579; L. E. Overman, A. E. Renaldo, *J. Am. Chem. Soc.* **1990**, *112*, 3945.
[23] K. N. Houk, J. Gonzalez, Y. Li, *Acc. Chem. Res.* **1995**, *28*, 81; O. Wiest, K. A. Black, K. N. Houk, *J. Am. Chem. Soc*. **1994**, *116*, 10336.
[24] H. S. Aaron, C. P. Ferguson, *Tetrahedron Lett*. **1968**, 6191.
[25] R. Stahl, R. Galli, R. Güller, H.-J. Borschberg, *Helv. Chim. Acta*, **1994**, *77*, 2125.

Received August 18, 2003