109. Introduction of Amino Alcohols in the Ring-Opening Reaction of 3-Bromo-2,5-dimethylthiophene 1,1-Dioxide. A Short Diastereoselective Synthesis of Substituted 'Tetrahydrobenzo[*a*]pyrrolizidines' (= Octahydro-1*H*-pyrrolo[2,1-*a*]isoindoles) Using L-Prolinol

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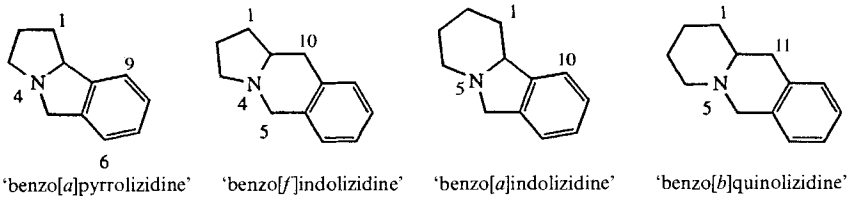
Dedicated to Prof. Dr. h.c. *Dieter Seebach* on the occasion of his 60th birthday

(16.I.97)

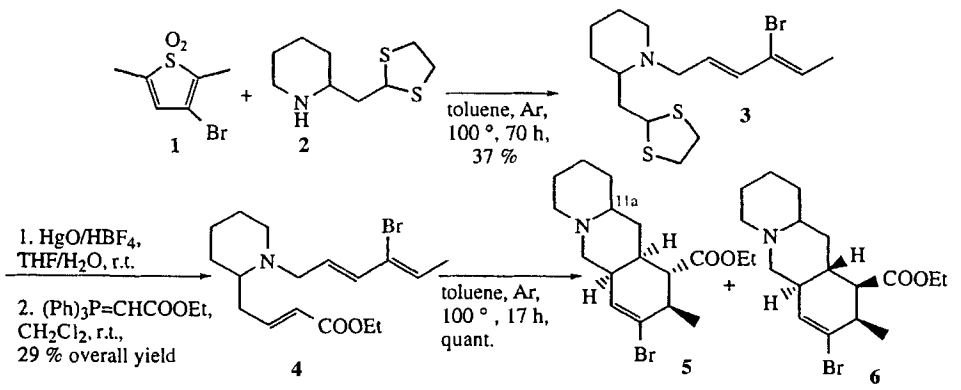
Tetrahydrobenzo[*a*]pyrrolizidines (= octahydro-1*H*-pyrrolo[2,1-*a*]isoindoles) and tetrahydrobenzo[*a*]indolizidines, (= decahydropyrido[2,1-*a*]isoindoles) were prepared stereoselectively in four steps through an amine-induced ring-opening of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**1**) with L-prolinol (**9**), piperidine-2-methanol (**10**), and piperidine-2-ethanol (**11**), yielding the dienes (2*S*)-1-[(2*E*,4*Z*)-4-bromohexa-2,4-dienyl]pyrrolidine-2-methanol (**12**), 1-[(2*E*,4*Z*)-4-bromohexa-2,4-dienyl]piperidine-2-methanol (**13**), and 1-[(2*E*,4*Z*)-4-bromohexa-2,4-dienyl]piperidine-2-ethanol (**14**; *Scheme 2*), which, after conversion into their α,β-unsaturated esters, cyclized in a $TiCl_4$-catalyzed intramolecular *Diels-Alder* reaction (*Scheme 3*). A discussion on the mechanism of the ring-opening reaction including semiempirical and *ab initio* calculations is also presented.

Introduction. – Pyrrolizidine alkaloids (PA) are found in a number of plant families, from which many traditional medicinal herbs are collected: *Apocynaceae*, *Asteraceae*, *Boraginaceae*, *Fabaceae*, and *Graminae*. PA are also found in herbivores living off these plants such as *Lepidoptera* (butterflies), some of which use PA as chemical defence against predators, and others transform them into pheromones. Indolizidine alkaloids (IA) are found in the *Swainsona* and *Astralagus* (american locoweed) species, in seeds from *Castanospermum australe*, *Ipomoea alba*, and *Ipomoea muricata*, and in leaves from *Elaeocarpaceae*. Quinolizidine alkaloids (QA) are found in *Adenocarpus hispanicus*, *Laburnocytsus adamii*, *Leontice leontopetalum*, *Lupinus albus*, and in numerous *Pearsonia species*. PA, IA, and QA are also detected in skin extracts from dendrobatid frogs [1–3]. Not only are these alkaloids found in a variety of fundamentally different organisms such as plants, fungi, insects, and animals, but many of them show pharmacologically relevant activities and, thereby, constitute attractive targets for synthesis. Indeed, a great number of syntheses has been described in the literature [1–3]. Enantioselective syntheses of PA have, *e.g.*, been achieved utilizing chiral building blocks such as L-proline derivatives, malic acids, and carbohydrates [1d]. Recently, we found that tetrahydrobenzo[*f*]indolizidines formerly, the fusion site was indicated by [*b*] instead of [*f*] and 'tetrahydrobenzo[*b*]quinolizidines' could be prepared through ring-opening of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**1**) using racemic 2-allylpyrrolidine, 2-allylpiperidine, 2-[(1,3-dithiolan-2-yl)methyl]pyrrolidine, and 2-[(1,3-dithiolan-2-yl)methyl]piperidine

(**2**) and a subsequent intramolecular *Diels-Alder* reaction, as illustrated for **1** and **2** in *Scheme 1* [4][1]).



Scheme 1



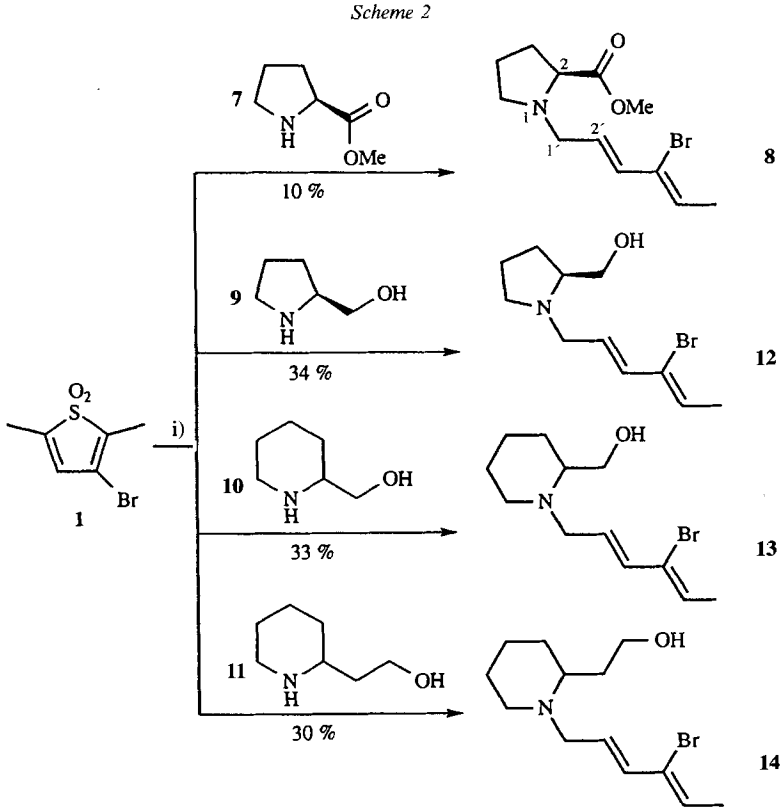
However, this protocol was limited by several drawbacks in its original version; *e.g.*, when using 2-allylpiperidine in the one-pot ring opening, the cyclized products were formed with poor stereoselectivity. Long reaction times were required for the (1,3-dithiolan-2-yl)methyl-substituted amines to ring-open **1**. The conversion of 1-[(2*E*,4*Z*)-4-bromohexa-2,4-dienyl]-2-[(1,3-dithiolan-2-yl)methyl]piperidine (**3**) into its corresponding α,β-unsaturated ester **4** was accomplished only in modest yield. However, the last step in the sequence showed promising features: quantitative yields and good stereoselectivities were observed when triene **4** was cyclized thermally; excellent stereoselectivities (*cis*/*trans* ratio 6:94) were obtained when catalyzing the intramolecular *Diels-Alder* addition with $TiCl_4$. This encouraged us to develop a new and general method for the synthesis of various PA, IA, and QA. In this paper, we introduce amino alcohols as versatile starting materials for the ring-opening reaction, and by using L-prolinol, five asymmetric centers could be formed stereoselectively in the final products.

Results and Discussion. – A new set of amines was initially considered for further investigations. *Shono et al.* [5], *Wistrand* and coworkers [6–8] and *Pedregal* and coworkers [9] have described procedures for synthesizing enantiomerically pure pyrrolidines starting from L-proline. First, we wanted to investigate if a methoxycarbonyl group at C(2) of the pyrrolidine ring was compatible with the conditions of the ring-opening

[1]) The *Diels-Alder* adducts **5** and **6** are depicted as products formed *via* dienophile addition from above the diene plane; this cyclization is possible for either of the enantiomers **4**, consequently the configuration at C(11a) is undefined in *Scheme 1*.

reaction, since this would simplify the amine synthesis and, more importantly, make it possible to introduce further substituents in the final products. However, when L-proline methyl ester (**7**) [10] was allowed to react with **1**, the yield of the desired product **8** was poor (10%) mainly because the cyclic amine polymerized (*Scheme 2*). Next, we tried the ring opening of cyclic amines substituted at C(2) with a hydroxymethyl group, since such methanols would by readily synthesized by reduction of the corresponding esters. L-Prolinol (**9**), piperidine-2-methanol (**10**), and piperidine-2-ethanol (**11**) were commercially available, and they all performed well in the ring-opening reaction which indeed became 2–3 times faster than is the case of 2-allylpyrrolidine or -piperidine, although the ring-opening reaction does not usually work in protic medium [11]. Thus, L-prolinol (**9**) gave (2*S*)-[(2*E*,*Z*)-4-bromohexa-2,4-dienyl]pyrrolidine-2-methanol (**12**) in 34% yield. Similarly the homologue **10** furnished the corresponding methanol **13** (33%) besides two major by-products, the isomeric 1-[(2*E*,4*Z*)-3-bromohexa-2,4-dienyl]piperidine-2-methanol (**27**; 4%) and 1-[(5-methyl-2-thienyl)methyl]piperidine-2-methanol *S*,*S*-dioxide (**26**; 3%) (see *Scheme 4* below for **26** and **27**). Finally, ethanol **11** reacted with **1** to give **14** in 30% yield. The by-products were analogous in all three cases, and they were formed in approximately the same amounts. Important to note is that **1** is stable in toluene at 100° for considerably longer periods than these reactions last, if no cyclic amine is present.

Scheme 2



i) Toluene, 100°, Ar.

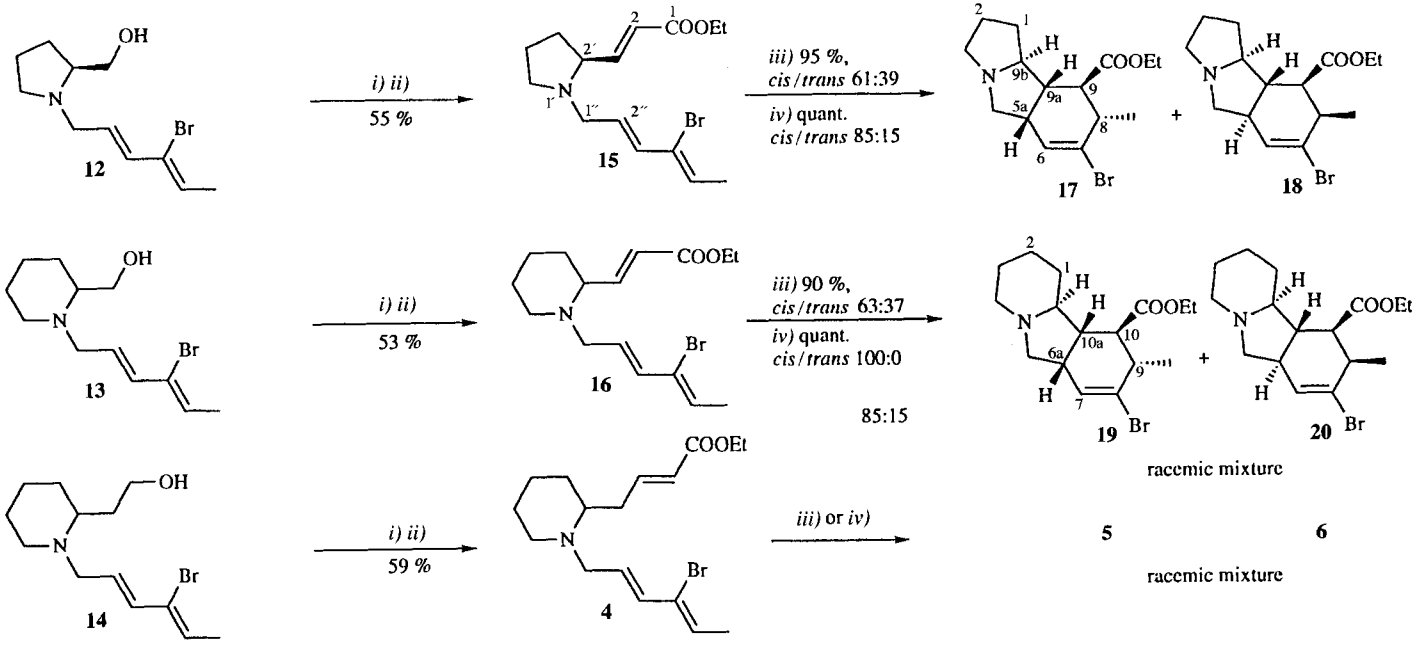
Following a *Swern-Wittig* protocol [12], the dienyl alcohols **12**–**14** could easily be transformed into the dienyl-substituted α,β-unsaturated esters **15**, **16**, and **4** (53–59%; *Scheme 3*). Ester **15** was also obtained in good overall yield (68%) from compound **8** by reduction with diisobutylaluminium hydride (DIBAL) to the corresponding aldehyde and subsequent condensation with $Ph_3P{=}CHOOEt$ [10].

Excellent yields and good stereoselectivities were observed when the trienes **15**, **16**, and **4** were cyclized thermally (*Scheme 3*): **15** gave the optically active 'tetrahydrobenzo[*a*]pyrrolizidines' **17** and **18** in 95% yield and a ratio 61:39, which corresponds to the *cis*/*trans* ratio at the fusion site. Similarly, **16** yielded the racemic 'tetrahydrobenzo[*a*]indolizines' **19** and **20** in 90% yield (*cis*/*trans* 63:37). The intramolecular cycloaddition of **4** to **5** and **6** has been described [4]. Quantitative yields and good-to-excellent stereoselectivities were obtained when these intramolecular *Diels-Alder* additions were catalyzed with $TiCl_4$: the *cis*/*trans* ratio was 85:15 in the case of **17** and **18** and 100:0 in the case of **19** and **20**. The adducts **17** and **19** are depicted as products formed *via* addition of the dienophile from below the diene plane, while **18** and **20** are depicted as products formed *via* addition of the dienophile from above the diene plane; according to semiempirical calculations, these are the favored cyclizations. The other *cis*- or *trans*-fused diastereoisomers will, therefore, be precluded in the intramolecular *Diels-Alder* addition, since they are formed *via* less favored transition states. Thus, this intramolecular addition becomes diastereoselective in the case of **15** [13].

Characterization of the addition products **17**–**20** was achieved through the use of gradient COSY, HETCOR, and NOESY techniques. In the ^{1}H-NMR spectra of **17** and **18**, the signals of H–C(6) and Me–C(8) were shifted downfield for the former. Also the ^{13}C-NMR signals of *C*OOEt, and *Me*–C(8) of **17** were shifted downfield as compared to those of **18**. This can be attributed to a γ-substituent effect [14]. Similar observations were made for **19** and **20**. We have already established that these trends are significant for *cis*-fused compounds [4]. NOESY Experiments confirmed that **17** and **19** were *cis*-fused while **18** and **20** were *trans*-fused intramolecular *Diels-Alder* adducts. In the NOESY of **17**, H–C(5a) and H–C(9a) correlated to each other as did H–C(9) to H–C(9b), H_{ax}–C(3), H_{ax}–C(5), Me–C(8). In the NOESY of **18**, H_a–C(5a) showed correlations to H–C(8) and H–C(9), and H_{ax}–C(5) correlated to H–C(9a).

During this work, we made observations with mechanistic implications. The ring-opening reaction is initiated by proton abstraction by the cyclic amine from either of the two Me groups in **1**. Abstraction from Me–C(5) yields a resonance-stabilized anion **A** (see *Fig.*) which initially will form a tight ion pair **21** with the ammonium ion (*Scheme 4*). The HOMO of anion *A* and the electrostatic charges of the carbon skeleton are concentrated to the methylene C-atom at C(5) (coeff. 0.33, charge −0.59), to C(4) (coeff. 0.54, charge −0.69), and to C(2) (coeff. 0.54, charge −0.44) (see *Fig.*); these are the positions where protonation should be expected. Furthermore, several minima on the potential-energy surface could be found for the tight ion pair, which suggests that the tautomerization could be described in terms of a conducted-tour mechanism analogous to the amine-mediated tautomerization of indene systems [15–20]. Protonation at C(2) will lead to the tautomer 3-bromo-2,5-dihydro-2-methyl-5-methylidenethiophene 1,1-dioxide (**22**) which is in fact thermodynamically favored over **1** by 1.79 kcal/mol. Yet, **22** was not been observed in the reaction mixture by either GLC or NMR and is, therefore, thought to react as soon as it is formed through an attack at the exocyclic methylene group by the amine, *i.e.*, by *Michael* addition to a vinyl sulfone [21–24]. Due to lack of β-substituents, **22** should be several orders of magnitude more reactive than **1** in such an addition [24].

Scheme 3



i) Swern oxidation: 1. CH_2Cl_2, −78°, Ar, $(COCl)_2$, DMSO; 2. Et_3N, 2 h, yield 75–80%. *ii) Wittig* reaction: CH_2Cl_2, r.t., $Ph_3P{=}CHCOOEt$, 1 h, yield 70–75%. *iii)* Thermal *Diels-Alder* reaction: toluene, Ar, 150°, 19–20 h, yield 90–95%. *iv)* $TiCl_4$-Catalyzed *Diels-Alder* reaction: 2 equiv. of $TiCl_4$, CH_2Cl_2, 0°, 7–9 days, quant. yield.

Not only does protonation of the intermediate anion favor the *cis*-2,5-disubstituted thiophene 1,1-dioxide **23** over the corresponding *trans*-isomer by 0.12 kcal/mol (calculated from the difference in transition-state energies), but the former also eliminates SO_2 on ring opening much faster than the latter yielding the main product **8**, **12**, **13**, or **14**. Since only the all-*trans*-diene with respect to the C-chain is formed, the ring-opening reaction has to occur *via* an intermediate *cis*-2,5-dihydrothiophene 1,1-dioxide [25] [26]. A *trans*-2,5-disubstituted isomer might also be formed but equilibrates with *cis*-isomer under basic conditions [27]. Compound **23** was not observed in the reaction mixture, neither by GLC nor NMR analyses.

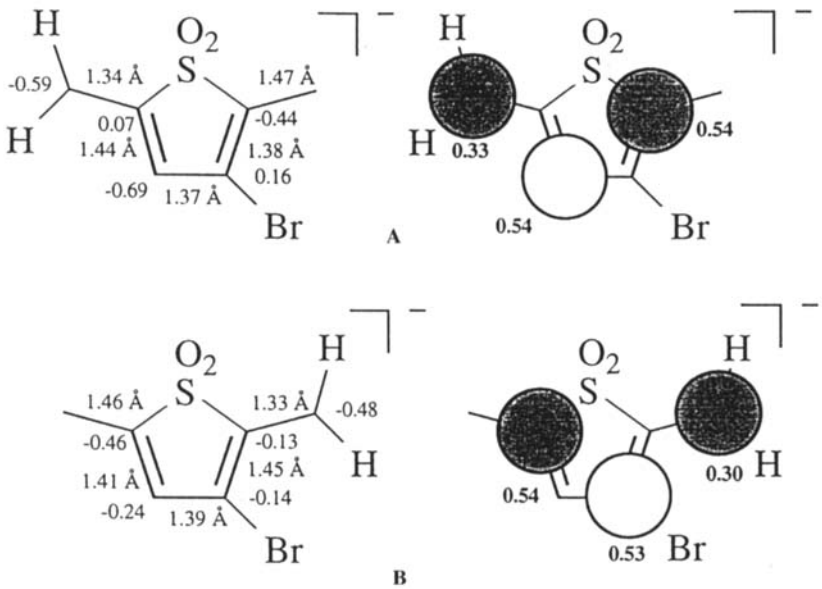
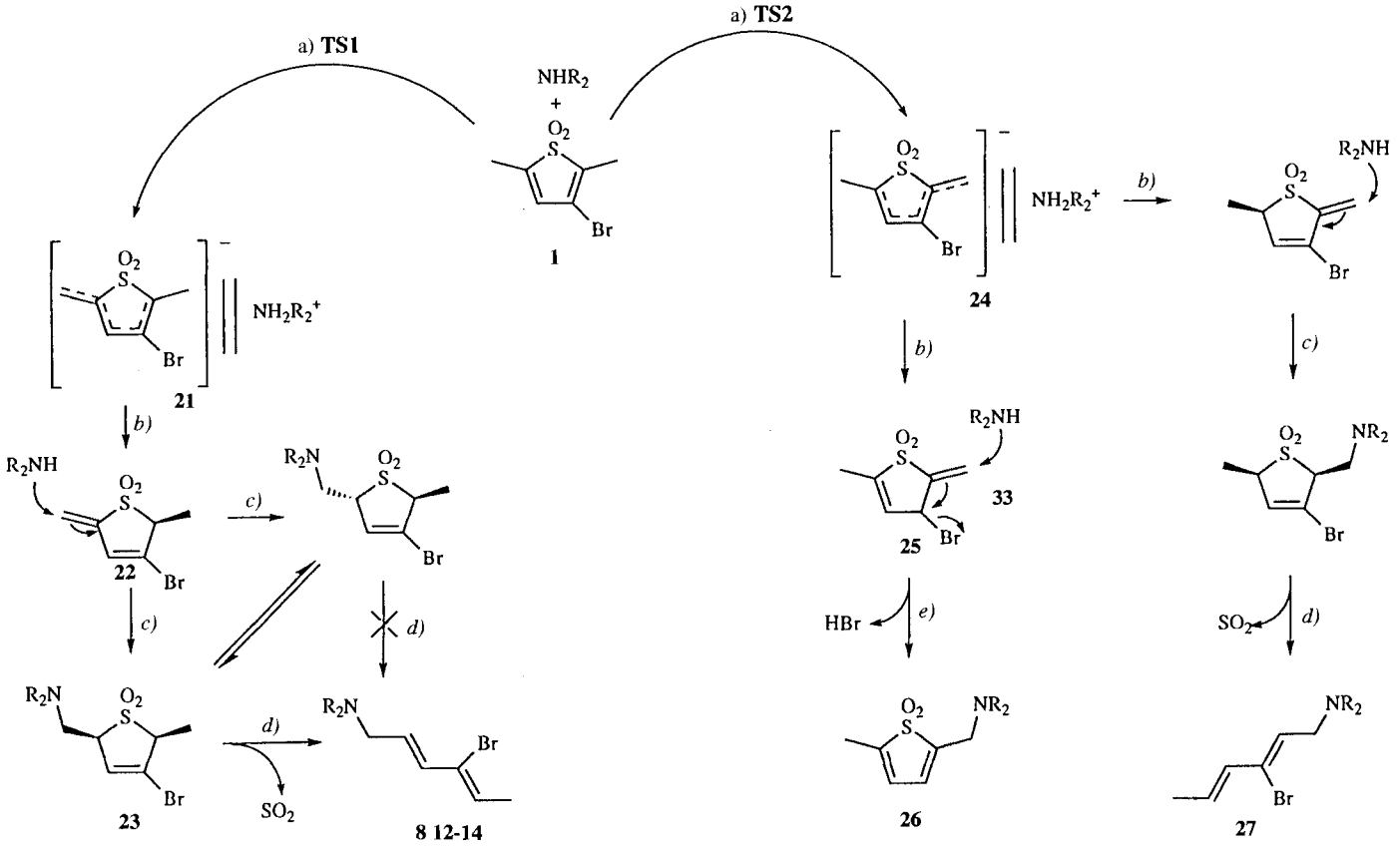


Figure. *Bond lengths and electrical charges* (left) *and HOMO signs and coefficients* (right) *calculated at the 3-21G(*) level for the anions* **A** *and* **B**

Formation of the ring-opening by-product **27** should follow the same mechanism, but after an initial proton abstraction at Me–C(2) of **1** yielding the ion pair **24** (*Scheme 4*). Calculations reveal a higher transition-state energy (TS1) by 1.65 kcal/mol for proton abstraction at Me–C(5) yielding **8** or **12**–**14** as compared to abstraction at Me–C(2) (TS2). This difference does not, however, reflect the selectivity seen in the final products; the selectivity is rather caused by the formation of a less stable anion **B** (by +5.68 kcal/mol as compared to **A**; *Fig.*) on deprotonation at Me–C(2). The charge of **B** is more evenly spread over the C-chain, while the HOMO corresponds to that of **A** (**B**: methylene C-atom at C(2), coeff. 0.30, charge −0.48; C(3), coeff. 0.53, charge −0.14; C(5); coeff. 0.54, charge −0.46; see *Fig.*). The relative instability of **B** makes it more prone to react by other mechanisms as well. *E.g.*, formation of the by-product **26** formed concomitantly with ring opening can be explained by protonation of C(3) in ion pair **24**, yielding an allyl bromide **25**, which in turn undergoes nucleophilic attack at the exocyclic methylene group in an S_N2' reaction. We believe that the large amount of unidentifiable by-products formed as a tar in the ring-opening reaction originates mainy from the decomposition of

Scheme 4. *Proposed Mechanism for the Ring-Opening Reaction and the Formation of Products and By-products*



a) b) Base-catalyzed tautomerization, *c) Michael* addition to vinyl sulfone: *d)* Disrotatory cheletropic elimination of SO_2. *e)* S_N2' attack on vinyl sulfone/allyl bromide.

the high-energy intermediate **24**: The rate enhancement caused by the presence of an OH group can in part emanate from a more facile tautomerization, in which the proton is transferred intramolecularly by the O-atom to the other side of the anion [22]. The rate-determining step for the ring-opening reaction seems, at this instance, to be the amine-mediated tautomerization of double bonds and not the *Michael* addition or the disrotatory cheletropic elimination. Further studies on the tautomerization are underway.

Conclusions. – The present reaction is a useful entry to the 'tetrahydrobenzo[*a*]-pyrrolizidine', 'tetrahydrobenzo[*f*]-' and 'tetrahydrobenzo[*a*]indolizidine', and 'tetrahydrobenzo[*b*]quinolizidine' structures. *cis*- or *trans*-fused products can be obtained stereoselectively either thermally or by $TiCl_4$ catalysis. Enantioselectivity, *i.e.*, the formation of five asymmetric centers can be achieved by using enantiomerically pure amines in the ring-opening reaction. Furthermore, we believe that the activating influence that the neighboring OH group exerts on the ring-opening of 3-bromo-2,5-dimethylthiophene 1,1-dioxide (**1**) has widened the scope of this new synthetic pathway considerably, both in respect to the amines and to the dioxides amenable for the reaction, a discovery that might prove a major breakthrough in the use of thiophene 1,1-dioxides as starting materials in a more general alkaloid synthesis.

Experimental Part

1. *General.* Semiempirical and *ab initio* calculations were made using SPARTAN [28] on a *Silicon Graphics* work station. Geometry optimizations for **1**, **22**, **A** and **B** and for the ion pairs **21** and **24** were performed using the PM3 force field. Transition-state searches for TS1 and TS2 and for the protonation of the intermediate *Michael*-addition adduct yielding **23** and its *trans*-2,5-disubstituted isomer respectively, were made; in all cases, one imaginary frequency corresponding to a transition-state vibration was found at the PM3 level. Ammonia was used as either amine or ammonium ion throughout the calculations. Single-point energy calculations, *i.e.* determination of energies, electrostatic charges, and MOs were made using the 3-21G(*) force field on the above calculated geometries. All solvents were distilled and purified according to standard procedures prior to use. CH_2Cl_2 was distilled from P_2O_5. The reagents DMSO and Et_3N were freshly distilled from CaH_2. Other commercial starting materials were used without further purification. Separations: *Chromatotron*™; rotors coated with *Merck* silica gel *60* (*60 PF_{254}*) containing gypsum. HPLC: semi-prep. *Nucleosil* silica-gel column (500 × 10 mm). GLC: *Varian-3600* gas chromatograph equipped with a *SPB5* capillary column. Optical rotations: *Perkin-Elmer-241* polarimeter. IR Spectra: *Perkin-Elmer-298 IR* spectrophotometer; ν in cm^{-1}. ^{1}H-NMR (400.13 MHz), ^{13}C-NMR (100.61 MHz), gradient COSY, HETCOR, and NOESY Spectra: *Bruker ARX400* instrument; δ in ppm rel. to residual solvent signals; J in Hz; $CDCl_3$ solns. MS: *Jeol-SX-102* mass spectrometer at 70 eV; *m/z* (rel. %).

2. *Synthesis of* **8** *and* **12**–**14**. *General Procedure for the Ring-Opening.* The soln. of thiophene dioxide [29] (1.115 g, 5.00 mmol) and amine **7** or **9**–**11** (20.00 mmol) in toluene (15 ml) was placed in an oil bath at 100° under Ar. After the reaction was complete (TLC or GLC monitoring), the mixture was diluted with Et_2O and washed with H_2O to remove the excess of **9**–**11**. The amines were then extracted with 1% HCl soln. the aq. phases made alkaline with 2M NaOH and extracted 3× with Et_2O, and the combined Et_2O phases dried ($MgSO_4$) and then evaporated to give an oil. The products were separated on a *Chromatotron*™ (heptane/AcOEt/Et_3N 90:5:5 for **8**, heptane/Et_2O/Et_3N/MeOH 60:40:1:5 for **12**–**14**). Anal. samples were obtained by HPLC (heptane/AcOEt/Et_3N 90:5:5 for **8**, heptane/AcOEt/Et_3N/MeOH 50:50:5:5 for **12**–**14**).

Methyl (2S)-1-[(2E,4Z)-4-Bromohexa-2,4-dienyl]pyrrolidine-2-carboxylate (**8**). Reaction of **1** with **7**: after 22 h more amine (1.0 g, 7.75 mmol) was added. After 48 h, **1** was consumed 145.9 mg (10%) of **8**. $[\alpha]_D = -34.64$ ($c = 3.9$, $CHCl_3$). IR (film): 1725*s* (C=O), 950*m*. ^{1}H-NMR: 6.14 (*d*, $J = 14.9$, H–C(3′)); 6.05 (*dt*, $J = 14.9$, 6.5, H–C(2′)); 5.95 (*q*, $J = 6.7$, H–C(5′)); 3.68 (*s*, MeO); 3.33 (*dd*, $J = -13.6$, 6.5, 1 H–C(1′)); 3.22 (*dd*, $J = -13.6$, 6.5, 1 H–C(1′)); 3.14 (*m*, H–C(2)); 3.11 (*m*, $J = 8.5$, H_{eq}–C(5)); 2.35 (*dd*, $J = 8.5$, H_{ax}–C(5)); 2.2–1.7 (*m*, CH_2(3), CH_2(4)); 1.83 (*d*, $J = 6.7$, Me(6′)). ^{13}C-NMR: 174.58 (COOMe); 131.73 (C(3′)); 130.06 (C(2′)); 128.60 (C(5′)); 125.78 (C(4′)); 65.44 (MeO); 55.93 (C(1′)); 53.74 (C(5)); 51.94 (C(2)); 29.57 (C(3)); 23.14 (C(4));

17.20 (C(6')). HR-MS: 287.0549 ($C_{12}H_{18}Br^+NO_2$; calc. 287.0557). MS: 287/289 (5, M^+), 228/230 (100), 208 (43), 159/161 (26), 70 (100).

(2S)-1-[(2E,4Z)-4-Bromohexa-2,4-dienyl]pyrrolidine-2-methanol (**12**). Reaction time 3 h: 442 mg (34%) of **12**. $[\alpha]_D = -37.40$ ($c = 3.7$, $CHCl_3$). IR (film): 3380 (br., OH), 1640*m* (C=C stretch., conjug. diene), 940*s* (CH bend., *trans*-RCH=CHR). ^{1}H-NMR: 6.20 (*d*, $J = 14.9$, H–C(3')); 6.08 (*dt*, $J = 14.9$, 6.2, H–C(2')); 6.00 (*q*, $J = 6.8$, H–C(5')); 3.65 (*dd*, $J = -11.0$, 3.4, 1 H, CH_2OH); 3.54 (*dd*, $J = -13.9$, 5.9, 1 H–C(1')); 3.45 (*dd*, $J = -11.0$, 3.1, 1 H, CH_2OH); 3.15 (*m*, $J = 8.6$, H_{eq}–C(5)); 3.09 (*dd*, $J = -14.0$, 7.4, H–C(1')); 2.35 (*q*, $J = 8.6$, H_{ax}–C(5)); 2.71 (*m*, $J = 9.0$, 3.4, 3.1, 1 H–C(2)); 1.87 (*d*, $J = 6.7$, Me(6')); 1.95–1.70 (*m*, CH_2(3), CH_2(4)). ^{13}C-NMR: 132.19 (C(3')); 130.39 (C(2')); 129.25 (C(5')); 126.18 (C(4')); 64.74 (C(2)); 62.43 (CH_2OH); 55.79 (C(1')); 54.72 (C(5)); 28.08 (C(3)); 23.95 (C(4)); 17.65 (C(6')). HR-MS (CI, pos. mode): 260.0635 ($C_{11}H_{19}Br^+NO$; calc. 260.0585). MS: 259/261 (< 1, $[M^+ - H]^+$), 228/230 (97), 159/161 (60), 70 (100).

1-[(2E,4Z)-4-Bromohexa-2,4-dienyl]piperidine-2-methanol (**13**). Reaction time 2 h: 452 mg (33%) of **13**, 55 mg (4%) of **27**, and 39 mg (3%) of **26**.

13: IR (film): 3400 (br. OH), 1650*m* (C=C stretch., conjug. diene), 950*s* (CH bend., *trans*-RCH=CHR). ^{1}H-NMR: 6.17 (*d*, $J = 15.0$, H–C(3')); 6.08 (*dt*, $J = 15.0$, 5.6, H–C(2')); 5.95 (*q*, $J = 6.8$, H–C(5')); 3.81 (*dd*, $J = -10.9$, 4.2, 1 H, CH_2OH); 3.52 (*dd*, $J = -14.6$, 5.7, 1 H–C(1')); 3.46 (*dd*, $J = -10.9$, 3.4, 1 H, CH_2OH); 3.12 (*dd*, $J = -14.6$, 7.7, 1 H–C(1')); 2.94 (*dt*, $J = 8.4$, 3.5, H_{eq}–C(6)); 2.38 (*m*, $J = 9.0$, 4.2, 3.4, H–C(2)); 2.25 (*ddd*, $J = -10.5$, 2.9, H_{ax}–C(6)); 1.88 (*d*, $J = 6.8$, Me(6')); 1.8–1.3 (*m*, CH_2(3), CH_2(4), CH_2(5)). ^{13}C-NMR: 132.05 (C(3')); 130.62 (C(2')); 128.77 (C(5')); 126.14 (C(4')); 62.93 (CH_2OH); 60.80 (C(2)); 55.14 (C(1')); 52.01 (C(6)); 28.30 (C(3)); 25.10 (C(5)); 24.03 (C(4)); 17.62 (C(6')). HR-MS: 273.0728 ($C_{12}H_{20}Br^+NO$; calc. 273.0728).

1-[(2E,4Z)-3-Bromohexa-2,4-dienyl]piperidine-2-methanol (**27**; R–R = $(CH_2)_4CH(CH_2OH)$). ^{1}H-NMR: 6.08 (*d*, *dq*, $J = 15.1$, 7.4, H–C(4'), H–C(5')); 5.97 (*t*, $J = 6.9$, H–C(2')); 3.79 (*dd*, $J = -10.9$, 4.2, 1 H, CH_2OH); 3.62 (*dd*, $J = -15.4$, 5.8, 1 H–C(1')); 3.49 (*dd*, $J = -10.9$, 3.8, 1 H, CH_2OH); 3.40 (*dd*, $J = -15.4$, 6.9, 1 H–C(1')); 2.96 (*dt*, H_{eq}–C(6)); 2.41 (*m*, H–C(2)); 2.34 (*ddd*, H_{ax}–C(6)); 1.85 (*d*, $J = 7.4$, 3 Me(6')); 1.75–1.25 (*m*, CH_2(3), CH_2(4), CH_2(5)). ^{13}C-NMR: 131.37 (C(2')); 130.44 (C(4')); 128.22 (C(5')); 127.00 (C(3')); 62.85 (CH_2OH); 60.89 (C(2)); 54.56 (C(1')); 52.19 (C(6)); 27.88 (C(3)); 24.89 (C(5)); 23.87 (C(4)); 18.01 (C(6')). MS: 273/275 (< 2, M^+), 242/244 (100), 159/161 (35), 84 (90).

1-[(5-Methyl-2-thienyl)methyl]piperidine-2-methanol S,S-Dioxide (**26**; R–R = $(CH_2)_4CH(CH_2OH)$): ^{1}H-NMR: 6.51 (H–C(3')); 6.31 (H–C(4')); 3.92 (*d*, $J = -15.9$, 1 H, CH_2–C(2')); 3.77 (*dd*, $J = -11.4$, 3.9, 1 H, CH_2OH); 3.57 (*dd*, $J = -11.4$, 4.8, 1 H, CH_2OH); 3.52 (*d*, $J = -15.9$, 1 H, CH_2–(2')); 3.02 (*dt*, H_{eq}–C(6)); 2.51 (*m*, H–C(2)); 2.36 (*ddd*, H_{ax}–C(6)); 2.12 (*d*, Me–C(5)); 1.8–1.2 (*m*, CH_2(3), CH_2(4), CH_2(5)). ^{13}C-NMR: 141.76 (C(2')); 141.34 (C(5')); 125.45 (C(3')); 122.31 (C(4')); 62.93 (CH_2OH); 61.04 (C(2)); 52.03 (C(6)); 49.00 (CH_2–C(2')); 27.08 (C(3)); 24.29 (C(5)); 23.50 (C(4)); 9.82 (C(6')). MS: 257 (< 2, M^+), 226 (100), 163 (5), 83 (25).

1-[(2E,4Z)-4-Bromohexa-2,4-dienyl]piperidine-2-ethanol (**14**). Reaction time 2 h: 432 mg (30%) of **14**. IR (film): 3400 (br., OH), 1650*m* (C=C stretch., conjug. diene), 950*s* (CH bend., *trans*-RCH=CHR). ^{1}H-NMR: 6.16 (*d*, $J = 14.7$, H–C(3')); 6.05 (*dt*, $J = 14.7$, 7.1, 5.7, H–C(2')); 5.98 (*q*, $J = 7.1$, H–C(5')); 3.91 (*dt*, $J = -11.0$, 1 H, CH_2CH_2OH); 3.73 (*dt*, $J = -11.0$, 1 H, CH_2CH_2OH); 3.61 (*dd*, $J = -14.0$, 5.7, 1 H–C(1')); 3.18 (*dd*, $J = -14.0$, 7.1, 1 H–C(1')); 2.98 (*m*, H_{eq}–C(6)); 2.64 (*m*, H–C(2)); 2.2 (*m*, H_{ax}–C(6)); 1.86 (*d*, $J = 7.1$, Me(6')); 1.83–1.35 (*m*, CH_2(3), CH_2(4), CH_2(5), CH_2CH_2OH). ^{13}C-NMR: 131.82 (C(3')); 130.15 (C(2')); 128.36 (C(5')); 125.88 (C(4')); 61.57 (CH_2CH_2OH); 59.26 (C(2)); 54.74 (C(1')); 50.63 (C(6)); 31.75 (CH_2CH_2OH); 28.04 (C(3)); 23.51 (C(5)); 22.99 (C(4)); 17.19 (C(6')). HR-MS: 287.0885 ($C_{13}H_{22}Br^+NO$; calc. 287.0885).

3. *Synthesis of* **4**, **15**, *and* **16**. *General Procedure for the* Swern *Oxidation of the* Wittig *Reaction* [12]. Oxalyl chloride (1.21 mmol, 104 µl) was dissolved in CH_2Cl_2 (8.0 ml) at –78° under Ar. DMSO (2.39 mmol, 170 µl) in CH_2Cl_2 (2.0 ml) was added dropwise *via* a syringe. Compound **12**, **13**, or **14** (1.00 mmol) in CH_2Cl_2 (6.0 ml) was injected 10 min later; the mixture was stirred for 35 min before Et_3N (4.94 mmol, 690 µl) was added. After 40 min at –78°, Ph_3P=CHCOOEt (1038 mg, 2.99 mmol), in CH_2Cl_2 (5 ml) was poured into the mixture, which was then allowed to reach r.t. within 2 h. The mixture was washed with a pH 7 buffer and H_2O ($MgSO_4$), and evaporated: **15**, **16**, or **4** in 53–59% overall yield after separation on a *Chromatotron*™ (heptane/AcOEt/Et_3N 90:5:5). Although this gave very pure products, the anal. samples were obtained after HPLC (heptane/AcOEt/Et_3N 75:25:5).

Ethyl (E)-3-{(2S)-1-[(2E,4Z)-4-Bromohexa-2,4-dienyl]pyrrolidin-2-yl}prop-2-enoate (**15**). Yield: 180.69 mg (55%). $[\alpha]_D = -68.23$ ($c = 0.15$, $CHCl_3$). IR (film): 1710*s* (C=O), 1645*m* (C=C stretch., conjug. diene), 950*s* (CH bend., *trans*-RCH=CHR). ^{1}H-NMR: 6.83 (*dd*, $J = 15.6$, 8.0, H–C(3)); 6.15 (*d*, $J = 14.8$, H–C(3")); 6.06 (*dt*, $J = 14.8$, 6.7, H–C(2")); 5.96 (*q*, $J = 6.7$, H–C(5")); 5.92 (*d*, $J = 15.6$, H–C(2)); 4.15 (*q*, $J = 7.1$, $MeCH_2O$); 3.43 (*dd*, $J = -13.8$, 6.7, 1 H–C(1")); 3.13 (*t*, $J = 8.4$, H_{eq}–C(5')); 2.95 (*q*, $J = 8.0$, H–C(2')); 2.85

(*dd*, $J = -13.8$, 6.7, 1 H–C(1″)); 2.22 (*dd*, $J = 8.4$, H_{ax}–C(5′)); 1.99 (*m*, H_{eq}–C(3′)); 1.85 (*d*, $J = 6.7$, Me(6″)); 1.81 (*m*, H_{eq}–C(4′)); 1.76 (*m*, H_{ax}–C(4′)); 1.67 (*m*, H_{ax}–C(3′)); 1.28 (*t*, $J = 7.1$, *Me*CH_2O). ^{13}C-NMR: 166.80 (C(1)); 150.62 (C(3)); 131.64 (C(3″)); 131.13 (C(2″)); 128.78 (C(5″)); 126.41 (C(4″)); 122.53 (C(2)); 66.06 (C(2′)); 60.74 (Me*C*H_2O); 55.63 (C(1″)); 54.07 (C(5′)); 31.82 (C(3′)); 23.12 (C(4′)); 17.60 (C(6″)); 14.66 (*Me*CH_2O). HR-MS: 327.0828 ($C_{15}H_{22}Br^+NO_2$; calc. 327.0834).

*Ethyl (*E*)-3-{1-[(2*E*,4*Z*)-4-Bromohexa-2,4-dienyl]piperidin-2-yl}prop-2-enoate* (**16**). Yield: 235.28 mg, (53%). IR (film): 1715*s* (C=O), 1650*m* (C=C stretch., conjug. diene), 950*s* (CH bend., *trans*-RCH=CHR). ^{1}H-NMR: 6.92 (*dd*, $J = 15.7$, 8.9, H–C(3)); 6.12 (*d*, $J = 14.9$, H–C(3″)); 6.04 (*dt*, $J = 14.9$, 6.1, H–C(2″)); 5.96 (*q*, $J = 6.8$, H–C(5″)); 5.92 (*dd*, $J = 15.7$, 0.7, H–C(2)); 4.18 (*q*, $J = 7.1$, MeCH_2O); 3.38 (*dd*, $J = -14.3$, 4.9, 1 H–C(1″)); 2.93 (*dt*, $J = -11.0$, H_{eq}–C(6′)); 2.83 (*dd*, $J = -14.3$, 7.3, 1 H–C(1″)); 2.80 (*m*, H–C(2′)); 2.00 (*dd*, $J = -11.0$, 3.0, H_{ax}–C(6′)); 1.86 (*d*, $J = 6.7$, Me(6″)); 1.8–1.4 (*m*, CH_2(3′), CH_2(4′), CH_2(5′)); 1.29 (*t*, $J = 7.1$, *Me*CH_2O). ^{13}C-NMR: 166.37 (C(1)); 151.16 (C(3)); 131.90 (C(3″)); 130.05 (C(2″)); 128.25 (C(5″)); 125.96 (C(4″)); 121.98 (C(2)); 64.21 (C(2′)); 60.39 (Me*C*H_2O); 57.59 (C(1″)); 52.06 (C(6′)); 32.73 (C(3′)); 25.57 (C(5′)); 23.45 (C(4′)); 17.19 (C(6″)); 14.24 (*Me*CH_2O). HR-MS: 341.0970 ($C_{16}H_{24}Br^+NO_2$; calc. 341.0990).

4. *Synthesis of* **17**–**20**. *Thermal Intramolecular* Diels-Alder *Addition*. Triene **15** (92.85 mg, 0.2829 mmol) or **16** (91.71 mg, 0.2679 mmol) was dissolved in toluene (50 ml) in a 100-ml glass ampoule which repeatedly was evacuated and flushed with Ar before it was sealed and immersed in an oil bath thermostated at 150° for 22 (**15**) or 20 h (**16**). Evaporation gave **17**/**18** 61:39 (88.17 mg, 95%) and **19**/**20** 63:37 (82.54 mg, 90%), resp.

The *cis*- and *trans*-fused products were separated by HPLC (heptane/AcOEt/Et_3N/MeOH 40:60:5:1 for **17** and **18** and heptane/AcOEt/Et_3N 75:25:5 for **19** and **20**).

*Ethyl (5a*R*,8*S*,9*R*,9a*S*,9b*S*)-*cis*-7-Bromo-2,3,5,5a,8,9,9a,9b-octahydro-8-methyl-1*H*-pyrrolo[2,1-a]isoindole-9-carboxylate* (**17**): $[\alpha]_D \approx -18.2$ (*c* = 0.506, $CHCl_3$). IR (film): 1725*s* (C=O). ^{1}H-NMR: 6.10 (H–C(6)); 4.21 (*q*, $J = 7.2$, MeCH_2O); 3.32 (H–C(9b)); 3.16 (H_{eq}–C(3)); 2.95 (H_{eq}–C(5)); 2.75 (H_{ax}–C(5)); 2.72 (H–C(5a)); 2.70 (*m*, $J = 7.5$, H–C(8)); 2.50 (H_{ax}–C(3)); 2.38 (H–C(9)); 2.24 (H–C(9a)); 2.03 (H_{eq}–C(1)); 1.79 (H_{eq}–C(2)); 1.70 (H_{ax}–C(2)); 1.37 (H_{ax}–C(1)); 1.29 (*t*, $J = 7.2$, *Me*CH_2O); 1.20 (*d*, $J = 7.5$, Me–C(8)). ^{13}C-NMR: 175.07 (*C*OOEt); 129.37 (C(7)); 128.71 (C(6)); 68.76 (C(9b)); 61.16 (Me*C*H_2O); 59.45 (C(5)); 56.63 (C(3)); 51.21 (C(9)); 46.72 (C(9a)); 39.44 (C(5a)); 39.33 (C(8)); 33.72 (C(1)); 26.82 (C(2)); 20.38 (*Me*–C(8)); 14.79 (*Me*CH_2O). HR-MS: 327.0829 ($C_{15}H_{22}Br^+NO_2$; calc. 327.0834). MS: 327/329 (3, M^+), 248 (40), 83 (100).

*Ethyl (5a*S*,8*R*,9*R*,9a*S*,9b*S*)-*trans*-7-Bromo-2,3,5,5a,8,9,9a,9b-octahydro-8-methyl-1*H*-pyrrolo[2,1-a]isoindole-9-carboxylate* (**18**): $[\alpha]_D = -2.4$ (*c* = 0.331, $CHCl_3$). IR (film): 1725*s* (C=O). ^{1}H-NMR: 5.88 (H–C(6)); 4.14 (*q*, $J = 7.2$, Me*C*H_2O); 3.41 (H–C(9b)); 3.05 (H_{eq}–C(3)); 3.39 (H_{eq}–C(5)); 2.98 (H–C(5a)); 2.83 (H–C(9)); 2.82 (*m*, $J = 7.0$, H–C(8)); 2.56 (H_{ax}–C(3)); 2.39 (H_{ax}–C(5)); 1.98 (H_{eq}–C(1), H_{eq}–C(2)); 1.87 (H–C(9a)); 1.86 (H_{ax}–C(1), H_{ax}–C(2)); 1.28 (*t*, $J = Me$*C*H_2O); 0.96 (*d*, $J = 7.0$, Me–C(8)). ^{13}C-NMR: 172.34 (*C*OOEt); 133.87 (C(6)); 120.30 (C(7)); 68.79 (C(9b)); 60.79 (Me*C*H_2O); 58.75 (C(5)); 55.04 (C(3)); 52.26 (C(5a)); 47.96 (C(9)); 47.34 (C(9a)); 36.48 (C(8)); 32.98 (C(1)); 28.40 (C(2)); 17.43 (*Me*–C(8)); 14.67 (*Me*CH_2O). HR-MS: 327.0832 ($C_{15}H_{22}Br^+NO_2$; calc. 327.0834). MS: 327/329 (5, M^+), 248 (37), 83 (100).

*Ethyl (6a*R**,9*S**,10*R**,10a*S**,10b*S**)-cis-8-Bromo-1,2,3,4,6,6a,9,10,10a,10b-decahydro-9-methylpyrido[2,1-a]-isoindole-10-carboxylate* (**19**): IR (film): 1725*s* (C=O). ^{1}H-NMR: 6.13 (H–C(7)); 4.15 (*q*, $J = 7.2$, Me*C*H_2O); 2.98 (H_{eq}–C(4)); 2.93 (H_{eq}–C(6)); 2.89 (*m*, $J = 7.5$, H–C(9)); 2.65 (H–C(10)); 2.43 (H–C(6a)); 2.40 (H_{ax}–C(4)); 2.11 (H_{ax}–C(6)); 1.98 (*m*, H–C(10a)); 1.80 (*m*, H_{eq}–C(2), H–C(10b)); 1.77 (*m*, H_{eq}–C(1)); 1.58 (CH_2(3)); 1.38 (H_{ax}–C(1)); 1.28 (*t*, $J = 7.2$, *Me*CH_2O); 1.17 (*d*, $J = 7.5$, Me–C(9)); 1.12 (*m*, H_{ax}–C(2)). ^{13}C-NMR: 171.89 (C(11)); 129.60 (C(7)); 127.14 (C(8)); 66.58 (C(10b)); 60.34 (Me*C*H_2O); 53.45 (C(10)); 52.91 (C(4)); 48.06 (C(6)); 44.61 (C(6a)); 41.92 (C(10a)); 41.11 (C(9)); 30.54 (C(1)); 26.01 (C(3)); 24.39 (C(2)); 16.49 (*Me*–C(9)); 14.18 (*Me*CH_2O). HR-MS: 341.0994 ($C_{16}H_{24}Br^+NO_2$; calc. 341.0990). MS: 341/343 (10, M^+), 262 (100), 97 (92).

*Ethyl (6a*R**,9*S**,10*S**,10a*R**,10*R**)-*trans*-8-Bromo-1,2,3,4,6,6a,9,10,10a,10b-decahydro-9-methylpyrido[2,1-a]-isoindole-10-carboxylate* (**20**): IR (film): 1725*s* (C=O). ^{1}H-NMR: 6.10 (H–C(7)); 4.17 (*q*, $J = 7.2$, Me*C*H_2O); 3.18 (H_{eq}–C(6)); 3.07 (H_{eq}–C(4)); 2.86 (H–C(6a)); 2.72 (*m*, $J = 7.5$, H–C(9)); 2.29 (H–C(10)); 2.27 (H–C(10a)); 2.07 (H_{ax}–C(4)); 1.99 (H_{ax}–C(6)); 1.85 (H–C(10b)); 1.79 (H_{eq}–C(2)); 1.65 (H_{eq}–C(3)); 1.62 (H_{eq}–C(1)); 1.56 (H_{ax}–C(3)); 1.29 (*t*, $J = 7.2$, *Me*CH_2O); 1.26 (*m*, H_{ax}–C(1)); 1.23 (*m*, H_{ax}–C(2)); 1.20 (*d*, $J = 7.5$, Me–C(9)). ^{13}C-NMR: 173.07 (C(11)); 130.09 (C(8)); 127.81 (C(7)); 70.62 (C(10b)); 61.16 (Me*C*H_2O); 59.13 (C(6)); 53.11 (C(4)); 52.23 (C(10)); 43.80 (C(10a)); 39.45 (C(6a)); 38.11 (C(9)); 30.57 (C(1)); 25.50 (C(3)); 24.87 (C(2)); 20.01 (*Me*–C(9)); 14.68 (*Me*CH_2O). HR-MS: 341.0992 ($C_{16}H_{24}Br^+NO_2$; calc. 341.0990). MS: 341/343 (10, M^+), 262 (100), 97 (75).

Intramolecular Diels-Alder *Addition. $TiCl_4$-Catalyzed.* Triene **15** or **16** was dissolved in dry CH_2Cl_2 under Ar to form a 114.7 mM soln. with respect to both the triene and dodecane, which was used as internal standard.

A fresh 229.4 mM $TiCl_4$ soln. in CH_2Cl_2 was then prepared, also under Ar. Equivalent volumes (usually *ca.* 100 µl) of the reagent solns. were combined in an additional 2 ml of dry CH_2Cl_2 and stirred gently under Ar at −2.5 to 0°. Reaction times were 9 days (plus another two days at r.t.) for **15** and 7 days for **16**. Then $CHCl_3$ (2 ml) was added to the mixture which was then washed 3 × with 1% HCl soln. and once with 10% $NaHCO_3$ soln. The org. phase was dried ($MgSO_4$), filtered, and analyzed by capillary GLC. The solvents were removed by a gentle stream of Ar the products dissolved in $CHCl_3$, and their NMR spectra recorded and found to be identical to those given above for **17**–**20**. The conversion was total and the yields were quantitative for both trienes. The *cis*/*trans* ratios were 85:15 (**17**/**18**) and 100:0 for (**19**/**20**), resp.

We wish to thank Mr. *Einar Nilsson* for the mass analyses, Dr. *Carl-Magnus Andersson* for comments on the manuscript, and the *Swedish Natural Science Research Council* for supporting this work financially.

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