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Asymmetric Induction in the Amine-Induced Ring-Opening of 3-Bromo-5-ethyl-2-isopropylthiophene 1,1-Dioxide using L-Prolinol

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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The diastereomers {1-(2*S*)-[(2*R*)(3*E*,5*Z*)-5-bromo-7-methyl-3,5-octadien-2-yl]-tetrahydro-1*H*-pyrrol-2-yl}methanol (**6**) and {1-(2*S*)-[(2*S*)(3*E*,5*Z*)-5-bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1*H*-pyrrol-2-yl}methanol **7**) were formed in a 65:35 ratio from 3-bromo-5-ethyl-2-isopropylthiophene, 1,1-dioxide (**5**) and L-prolinol. (5*R*,5a*S*,8*R*,9*R*,9a*S*,9b*S*)-Ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate (**10**) and (5*S*,5a*S*,8*R*,9*R*,9a*S*,9b*S*)-ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate (**12**) were synthesized from **6** and **7** in order to establish the absolute configuration of the ring-opened products. The asymmetric induction at C(2) in the ring-opened products can be explained by the preferential formation of *E* tautomers over *Z* tautomers and the preferential formation of the *E*(2*S*) (**15**) and *Z*(2*S*) (**17**) enantiomers over the *E*(2*R*) (**14**) and *Z*(2*R*) (**16**) enantiomers when **5** tautomerizes. The tautomers form complexes with the L-prolinol dimers, and the enantiotopic face that will preferentially be attacked by another L-prolinol equivalent in a Michael addition will be the one *anti* to the dimer and *syn* to the isopropyl group.

In a previous paper we investigated which variables were important in the amine-induced ring-opening of thiophene 1,1-dioxides by use of multivariate optimization procedures.[1] We found that the molar ratio between the amine and the dioxide and their respective concentrations were the most important. The polarity of the solvent was crucial: low dielectric constants, low dipole moments and low E_t values were preferred properties. The reaction temperature proved to be an independent variable, and could be kept constant within a range. Deuterium-labelling experiments showed a small primary kinetic isotope effect when using 3-bromo-2-isopropyl-5-trideuteriomethylthiophene 1,1-dioxide in the ring-opening reaction, suggesting that the rate-determining step was the initial proton abstraction of the tautomerization process. A 5.25:1 molar ratio of reagents was found to be optimal. This, together with a strong concentration dependence, suggest that a complex between several amine molecules and a dioxide molecule is formed prior to the tautomerization, and that this complex is maintained during the tautomerization process and possibly until the Michael addition, i.e., the addition of the amine to the tautomerized exomethylene group. If this is true, what would happen if a chiral amine reacted with a 5-ethyl- instead of a 5-methyl-substituted dioxide? Would there be an asymmetric induction at C(2) in the ring-opened product? This question was the focus of the present investigation.

Results

The synthesis of the desired dioxide was a straightforward task: 2,3,5-tribromothiophene (**1**), was treated with *sec*-butyllithium and acetone and then refluxed with oxalic acid under reduced pressure to give 3,5-dibromo-2-isopropenylthiophene (**2**) in 74.5% yield.[2] Hydrogenation with Wilkinson's catalyst yielded 3,5-dibromo-2-isopropylthiophene (3) in 92%.[2] Treatment of **3** with *sec*-butyllithium and diethyl sulfate (**CAUTION:** Poison B; mutagenic, irritant) gave 3-bromo-5-ethyl-2-isopropylthiophene (**4**) in 80% yield. Oxidation of **4** with *meta*-chloroperbenzoic acid gave 3-bromo-5-ethyl-2-isopropylthiophene 1,1-dioxide (**5**) in 39% yield (Scheme 1).[3,4]

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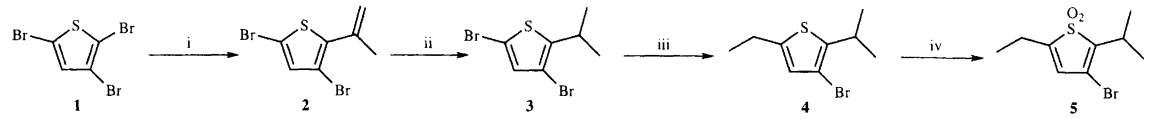


Scheme 1. i, (1) *s*-BuLi; (2) acetone; (3) $(COOH)_2$, yield 74.5%: ii, H_2–Wilkinson's catalyst, yield 92%, iii, (1) *s*-BuLi; (2) $(EtO)_2SO_2$, yield 80%: iv, mcpba, yield 39%.

Compound **5** had the required properties for this investigation: an isopropyl group in the 2-position, making tautomerization from that side more difficult; and an ethyl group at C(5), which would give an intermediate with an enantiotopic face after the tautomerization. Using the optimized reaction conditions found for the reaction of amino alcohols with 3-bromo-2-isopropyl-5-methylthiophene 1,1-dioxide – typically yielding more than 80% of the ring-opened product[1] – led to a drastic drop in yield when **5** was reacted with L-prolinol. Decreasing the temperature to 80 °C did not increase the yield to any great extent. A diastereomeric mixture of two ring-opened products was obtained in 29% total yield (Scheme 2). The diastereomers {(2*S*)-1-[(2*R*)(3*E*,5*Z*)-5-bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1*H*-pyrrol-2-yl}methanol (**6**) and {(2*S*)-1-[(2*S*)(3*E*,5*Z*)-5-bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1*H*-pyrrol-2-yl}methanol (**7**) were formed in a 65:35 ratio, which was constant over the temperature range investigated: 80–116 °C. Clearly, asymmetric induction had taken place. After conferring with an expert,[5] we were dissuaded from determining the absolute configuration at C(2) by circular dichroism. It would have been difficult to evaluate the CD spectra of **6** or **7**, since the chromophores were weak and the molecules were flexible. However, after transforming **6** and **7** into the trienes(*E*)-ethyl 3-{(2*S*)-1-(2*R* and 2*S*)(3*E*,5*Z*)-5-bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1*H*-pyrrol-2-yl}-2-propenoate (**8** and **9**) by using a Swern–Horner–Emmons protocol,[6,7] we were able to cyclize the products in a thermal intramolecular Diels–Alder reaction (IMDA). The Swern–Horner–Emmons reaction gave a 64% overall yield of **8** and **9**, and the IMDA gave a mixture of four components in 96% yield: **8** gave a mixture of **10** and **11** in a ratio of 86:14, while **9** gave a mixture of **12** and **13** in a ratio of 90:10. The relative configuration of these IMDA products could be determined through standard NMR techniques. Once determined, these configurations provided the necessary information for deducing the absolute configuration of **6**–**9**.

The IMDA isomers were separated by high performance liquid chromatography, and were distinguished and characterized through analysis of their respective COSY, HETCOR, HETCOR long-range and NOESY spectra.

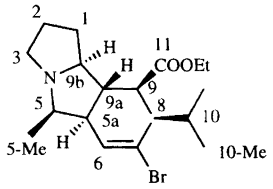
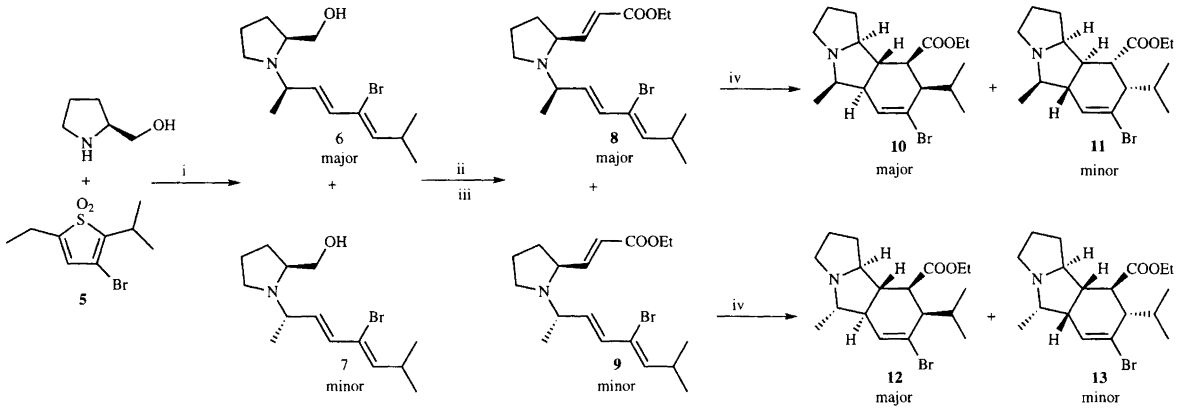


Fig. 1. trans-Fused IMDA product **10**.

Compound **10** (Fig. 1) was the major product from the cyclization of the major triene **8**. The NOESY correlation pattern for **10** was as follows: 5-Me correlated to 5-H, 6-H, 9a-H and 3-H_{eq}; 5a-H, 8-H and 9-H all correlated to each other; 9b-H correlated to 9-H and 1-H_{eq}. The coupling constant for 5-H, showing a quintet, was 7.2 Hz; the coupling constants for 5a-H were 11.4 and 7.2 Hz; the coupling constant for 9a-H, giving a quartet, was 11.4 Hz; a 11.4 Hz coupling constant was found for both 9b-H and 9-H; for 9-H, a double doublet, a 6.6 Hz coupling to 8-H was also observed. These couplings and NOESY patterns suggest that 5-H and



Scheme 2. i, ring-opening: *p*-xylene, argon, 90 °C, 2.5 h, 29%; ii, Swern oxidation: (1) CH_2Cl_2, −78 °C, argon, $(COCL)_2$, DMSO; (2) Et_3N, 2 h; iii. Horner–Emmons reaction: THF, NaH, $(EtO)_2POCH_2COOEt$, r.t., 1.5 h, 64% overall; iv. thermal Diels–Alder reaction: toluene, argon, 100–120 °C, 1–2 days, 96%.

5a-H are *cis* to each other; that 9a-H is *trans* to 5a-H, 9-H and 9b-H; and that 8-H and 9-H are *cis* to each other. Therefore, **10** is the *trans* fused isomer with a 5*R* configuration: (5*R*,5a*S*,8*R*,9*R*,9a*S*,9b*S*)-ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate, formed via addition of the dienophile form above the diene plane. Compound **12** was the major product from the cyclization of the minor triene **9**. The NOESY correlation pattern for **12** was as follows: 5-Me correlated to 5-H, 5a-H and 6-H; 5a-H, 8-H and 9-H correlated all to each other; 9b-H correlated to 1-H, 5a-H and 9-H. The coupling constants for 5-H were 6.0 Hz and 11.3 Hz; the coupling constant for 5a-H, showing a triplet, was 11.3 Hz; the coupling constant for 9a-H, giving a quartet, was 11.3 Hz; a 11.3 Hz coupling constant was also found for 9b-H and 9-H. These coupling and NOESY patterns suggest that 5-H and 5a-H are *trans* to each other; and that 9a-H is *trans* to 5a-H, 9-H and 9b-H. Therefore, **12** is the *trans* fused isomer with a 5*S* configuration: (5*S*,5a*S*,8*R*,9*R*,9a*S*,9b*S*)-ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate, formed via addition of the dienophile from above the diene plane. If we look at the dihedral angles between C(5-Me) and C(3), C(6) and C(9a), respectively, we should expect an upfield shift for C(5-Me), C(3) and C(6) and a downfield shift for C(9a) of several ppm in the ^{13}C NMR spectrum of compound **10** relative to compound **12**. Indeed, this was seen, which further supports the configurational assignments of these isomers. Compound **13** was the minor product from the cyclization of the minor triene **9**. In the ^{1}H NMR spectra of **13** and **12** the signal of 10-CH was shifted downfield for the former. Also, the carbons C(10) and C(11) were shifted downfield in the ^{13}C NMR spectrum of **13**, which can be attributed to a γ-substituent effect.[8] We have seen in previous work that these trends are significant for *cis* fused compounds.[4] In the NOESY of **13**, 5a-H correlated to 5-H, 5-Me, 6-H and 9a-H. In addition, 5-Me correlated to both the 3-H protons and to 6-H. The coupling constants for 5-H were 6.6 and 5.9 Hz; the coupling constants for 5a-H were 5.9 and 7.3 Hz; the coupling constants for 9a-H were 12.1 and 7.3 Hz; in the absorption of 9-H two coupling constants were also found: 12.1 and 9.5 Hz; for 8-H a 9.5 Hz coupling constant was observed. This data establishes a *cis* relationship between 5-H and 5a-H and between 5a-H and 9a-H; and a *trans* relationship between 9a-H and 9-H and between 9-H and 8-H. These patterns imply that **13** is the *cis* fused isomer with a 5*S* configuration: (5*S*,5a*R*,8*S*,9*R*,9a*S*,9b*S*)-ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate, formed via addition of the dienophile from below the diene plane. Compound **11** was the minor product from the cyclization of the major triene **8**. Neither the proton nor the carbon shifts in the six-membered ring or in the isopropyl or the ethoxycarbonyl group of **11** differed significantly from the corresponding ones in **10**; there was no *cis*/*trans* relationship between the two compounds. In the NOESY spectrum of the former, 5-Me correlated to 3-H, 5-H and 5a-H; and 9a-H correlated to 5-H, the 10-Me groups and 9b-H. A 12.0 Hz coupling constant was found for 5-H, 5a-H, 9a-H and 9-H; an 8.0 Hz coupling constant was found for 9b-H and 9a-H; a 5.6 Hz coupling constant was found for 9-H and 8-H. These data establish a *trans* relationship between 5-H and 5a-H, between 5a-H and 9a-H and between 9a-H and 9-H; and a *cis* relationship between 9a-H and 9b-H and between 9-H and 8-H. The conclusion is that **11** is the *trans* fused isomer with a 5*R* configuration formed via addition of the dienophile from below the diene plane: (5*R*,5a*R*,8*S*,9*S*,9a*R*,9b*S*)-ethyl 7-bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1*H*-pyrrolo[2,1-*a*]isoindole-9-carboxylate.

Discussion

How do we explain the asymmetric induction in view of the proposed mechanism for the ring-opening reaction?[1,9] This is not easy, since we have to consider non-detectable intermediates and other transient structures. Although highly speculative, the discussion is warranted and might serve as a starting point for further investigation. In short, the ring-opening reaction is initiated by a proton abstraction at CH_2 (C5) in **5**; the proton is then transferred intramolecularly to C(2), which becomes protonated to give an ethylidene tautomer.[1] In this case, there are four possible ethylidene tautomers: *E*(2*R*) **14**, *E*(2*S*) **15**, *Z*(2*R*) **16** and *Z*(2*S*) **17** (Fig. 2). After addition of the amine to these vinyl sulfone analogues, an intermediate *cis* sulfolene is formed. The actual ring-opening is a disrotatory chelotropic elimination of SO_2* from *cis* sulfolene, because only *E*,*E* dienes[10,11] with respect to the carbon chain are formed (Scheme 3).[1,4,9,12–14] In a Michael addition to vinyl sulfones the reaction is second order in amine when benzene is the solvent, while it is first order in ethanol.[15] The authors argue that an extra amine molecule is needed in the transition state (TS); in ethanol a solvent molecule takes this role. They also confirm that the reaction

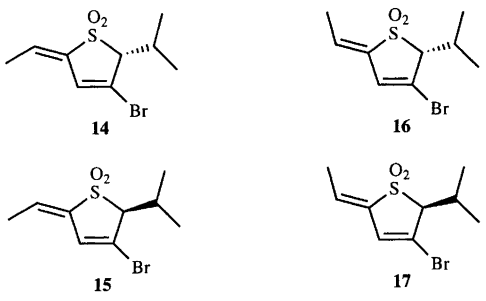
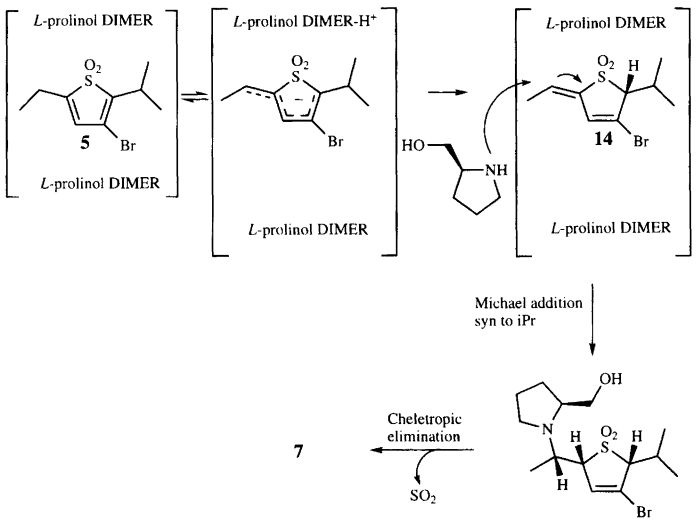


Fig. 2. The tautomers *E*(2*R*) **14**, *E*(2*S*) **15**, *Z*(2*R*) **16** and *Z*(2*S*) **17**.

* The formation of SO_2 has been established by trapping the evolved gas in a $KMnO_4$ solution and observing the formation of MnO_2.



Scheme 3. The tautomerization and ring-opening of **5**.

proceeds via an anionic TS.[16] Very negative activation entropies speak for a highly ordered transition state, sensitive to the steric demands of the reagents.[17] This implies that a free amine is favoured in the attack. Furthermore, a nucleophilic attack on a double bond proceeds with a tetrahedral attack angle of 109.5° (NC=C angle) and reaches the TS at a distance (N–C) of about 2 Å,[18–20] which means that L-prolinol approaches the tautomer from the outside and that the configuration at C(2) in the dioxide will have a small direct influence on the diastereoselectivity, since the energetics of steric interactions are proportional to r^{-6}. In a non-polar solvent such as *p*-xylene L-prolinol may form doubly hydrogen-bonded dimers, and in doing so it will gain some extra stabilization energy. Figure 3 shows such a dimer (**18**) with PM3-optimized geometry.[21] This dimer can form a weak complex with **5**, gaining 2.2 kcal mol^{-1} compared with the free dimer and the free dioxide. Adding another dimer on the other side of **5** also leads to some extra stabilization. A 2:1 complex is thus conceivable, where the hydrogen bonded dimers lie separated with the dioxide in between. An optimum molar ratio of reagents of 5.25:1 was found.[1] When proton abstraction occurs, the protonated dimer will necessarily come closer to the carbanion; the closer they get the more the configurational differences will manifest themselves. We therefore suspect that the asymmetric induction takes place when C(2) of the carbanion is protonated. Immediately after this protonation a complex such as **19**† exists. This complex between **18** and **14** (Fig. 4) is considerably closer than the one between **18** and **5**: the extra stabilization energy of 5.2 kcal mol^{-1} is mainly caused by an increase in electrostatic interactions, but probably also to some extent by increased charge transfer interactions.[22] An important observation made earlier was the high degree of deuterium incorporation at C(2) in the diene when 3-bromo-2-isopropyl-5-trideuteriomethyl-thiophene 1,1-dioxide was ring-opened; this indicates that the Michael addition takes place shortly after the tautomer formation and before any

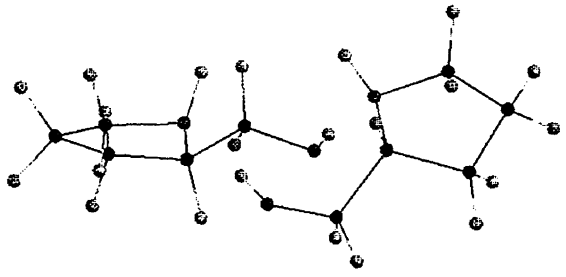


Fig. 3. The L-prolinol dimer (**18**).

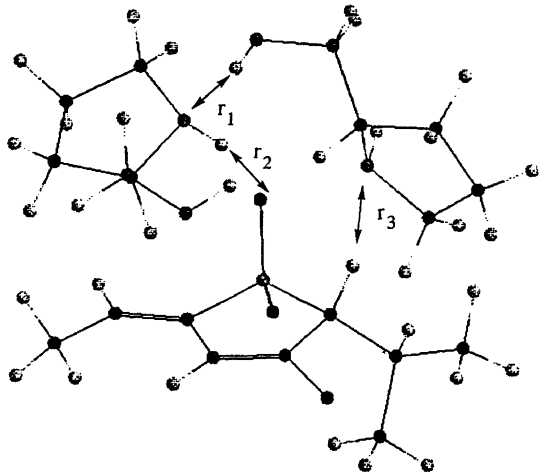


Fig. 4. Complex (**19**) between the L-prolinol dimer (**18**) and the *E*(2*S*) tautomer (**14**). r_1 = N–H(O) 1.84 Å; r_2 = (N)H–O(S) 2.70 Å; r_3 = N–H(C2) 2.78 Å.

† Complex **19** is the lowest of many low-energy conformations found when combining **18** and **14** in different ways; it is most likely not the lowest-lying conformation, but can serve as a model for discussion. Combining **18** *syn* to the isopropyl group of **14** led to the weakest complexes.

significant complex dissociation has occurred.[1] If **19** is more or less intact, another L-prolinol molecule can attack the tautomer from the opposite side, i.e., *syn* to the isopropyl group. The dimer will not only stabilize the build-up of negative charge in the transition state of the S_N2' reaction, it can also provide protons for the protonation of the intermediate α-sulfonyl carbanion, yielding a *cis* sulfolene. Cram's rule would favour an attack *anti* to the bulky complexing dimer, i.e., *syn* to the isopropyl group; and, in the context of a Michael addition with a highly ordered transition state *vide supra*,[17] an attack *syn* to the complexing L-prolinol moiety would be disfavoured. Consequently, we believe that the favoured attack is *anti* to the complexing dimer and *syn* to the isopropyl group, and that the asymmetric induction depends mainly on an unequal formation of tautomers.

The small primary kinetic isotope effect could be explained by assuming an early reactant-like transition state for the initial proton abstraction.[1] The energy difference between the pre-*E* and the pre-*Z* conformations is only about 0.3 kcal mol^{-1} in favour of the former; the *E* tautomer is also thermodynamically favoured by 1.1 kcal mol^{-1} over the *Z* tautomer. It is therefore likely that the *E* tautomers form preferentially, but in unequal amounts. Subsequently, the major diastereomer **6** is formed when **15** is attacked *syn* to the isopropyl group and *anti* to the complexing dimer, while the minor diastereomer **7** is formed when **14** is attacked *syn* to the isopropyl group and *anti* to the complexing dimer. The same line of argument can be applied to the reactions of the *Z* tautomers **16** and **17**, in which case the total reaction becomes more racemic.

Conclusions

The asymmetric induction at C(2) in the ring-opened products can be explained by the preferential formation of *E* tautomers over *Z* tautomers and the preferential formation of the *E*(2*S*) (**15**) and *Z*(2*S*) (**17**) enantiomers over the *E*(2*R*) (**14**) and *Z*(2*R*) (**16**) enantiomers. The tautomers form complexes with the L-prolinol dimers, and the enantiotopic face that will be preferentially attacked by another L-prolinol equivalent will be the one *anti* to the dimer and *syn* to the isopropyl group. The dimer stabilizes the negative charge in the TS of the Michael addition and protonates the α-sulfonyl carbanion to give a *cis* sulfolene. The *cis* sulfolene ring-opens to give an *E,E* diene with respect to the carbon chain exclusively.

Experimental

General. Semiempirical calculations were carried out using SPARTAN[21] on a Silicon Graphics Indy machine. Geometry optimizations for **5**, **14**, **16**, **18** and **19** were performed using the RHF/PM3 force field using default parametrization. The ^{1}H NMR (at 400.13 MHz), ^{13}C NMR (at 100.61 MHz), gradient COSY, HETCOR, HETCOR long-range and NOESY spectra were recorded on a Bruker ARX400 instrument; δ is in ppm relative to residual solvent signals; *J* is in Hz; Deuteriochloroform was consistently used as the solvent. The mass spectra were recorded on a JEOL-SX 102 mass spectrometer at 70 eV; *m/z* (rel. %). GLC analyses were carried out on a Varian 3600 gas chromatograph equipped with an SPB5 capillary column. The IR spectra were recorded on a Perkin–Elmer 298 infrared spectrophotometer; ν is in cm^{-1}. Optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter. Separations on a Chromatotron™ were made using rotors coated with Merck silica gel 60 (60 PF_{254}) containing gypsum. HPLC chromatography was performed on a semipreparative Nucleosil silica column (500 × 10 mm). All solvents were distilled and purified according to standard procedures prior to use. Dichloromethane was distilled from phosphorus pentoxide. The reagents dimethyl sulfoxide and triethylamine were freshly distilled from calcium hydride. Oxalyl chloride was distilled from 4 Å molecular sieves. Other commercial starting materials were used without further purification.

3,5-Dibromo-2-isopropenylthiophene (**2**).[2] *sec*-Butyllithium (26.9 ml, 1.3 M, 35 mmol) was added dropwise over 1 h to a solution of 2,3,5-tribromothiophene (**1**) (10.69 g, 33.0 mmol) in anhydrous ether (20 ml) under an argon atmosphere at −78 °C. After 30 min acetone (2.69 ml, 36.67 mmol) in anhydrous ether (7 ml) was added slowly; the reaction mixture was stirred for 40 min at −78 °C, and was then allowed to reach ambient temperature over 1 h. The reaction mixture was poured onto an ice–HCl slurry after which the water phase was extracted three times with ether and the combined ethereal layers were washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The crude product was refluxed for 1 h with oxalic acid (0.33 g) at 61–63 °C/1.50 Pa. Distillation under argon gave 6.95 g (74.5%) of the title compound; b.p. 104 °C/0.13 Pa. ^{1}H NMR: δ 6.92 (1 H, H-4), 5.48 (1 H, C=CH), 5.25 (1 H, C=CH) 2.15 (3 H, CH_3). ^{13}C NMR: δ 135.77, 133.69, 118.00, 110.54, 106.05, 23.62.

3,5-Dibromo-2-isopropylthiophene (**3**).[2] 3,5-Dibromo-2-isopropenylthiophene (**2**) (6.80 g, 24.1 mmol) was dissolved in a 4:1 mixture of toluene and heptane (63 ml) and $(PPh_3)_3RhCl$ (200 mg) was added; the flask was placed in a Parr hydrogenation apparatus and flushed three times with hydrogen. Complete hydrogenation was

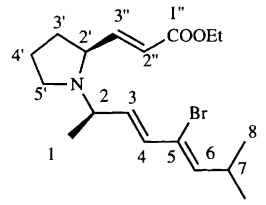


Fig. 5. Numbering for NMR assignments, see also Fig. 1.

achieved after 20 h at a working pressure of 3.2 kg cm^{-2}. After filtration through Celite the product was distilled under argon to give 6.30 g (92%) of the title compound, b.p. 66–68 °C/0.01 Pa. ^{1}H NMR: δ 6.94 (1 H, H-4), 3.33 [septet, 1 H, C*H*$(CH_3)_2$, *J*=6.9], 1.31 [d, 6 H, CH(C*H*$_3)_2$, *J*=6.9]. ^{13}C NMR: δ 149.30, 136.20, 109.22, 106.35, 30.67, 24.07.

3-Bromo-5-ethyl-2-isopropylthiophene (**4**). 3,5-Dibromo-2-isopropylthiophene (**3**) (4.9 g, 17.27 mmol) was dissolved in anhydrous ether (40 ml) and cooled to −78 °C under an argon atmosphere. 1.3 M *sec*-Butyllithium (13.70 ml, 17.83 mmol) was then added dropwise over 30 min. After 1 h diethyl sulfate (**CAUTION**) (2.80 ml, 21.39 mmol) in anhydrous ether (20 ml) was added via a syringe, and the reaction mixture was allowed to reach ambient temperature over 75 min. The reaction mixture was quenched with water and finally a large volume of 10% ammonia in ethanol was poured into the reaction vessel; this mixture was left overnight. The mixture was extracted several times with ether; the ethereal layers were washed with saturated ammonium chloride solution and water, dried over magnesium sulfate and evaporated *in vacuo* to give a 4:1 mixture of 5-alkylated:5-protonated thiophenes in quantitative yield. These were separated on a Chromatotron™ using heptane as the eluent to give 3.22 g (80%) of the title compound as an oil. ^{1}H NMR: δ 6.26 (t, 1 H, H-4, *J*=2.1), 3.10 [septet, 1 H, C*H*$(CH_3)_2$, *J*=7.1), 2.50 (dq, 2 H, CH_2, *J*=2.1, 7.0), 1.39 [d, 6 H, CH(C*H*$_3)_2$, *J*=7.1], 1.24 (t, 3 H, CH_2CH_3, *J*=7.0). ^{13}C NMR: δ 146.37 (C-2), 143.39 (C-5), 125.12 (C-4), 119.37 (C-3), 28.88 [*C*H$(CH_3)_2$], 19.66 [CH(*C*H$_3)_2$], 17.09 (*C*H_2CH_3), 10.73 (CH_2*C*H_3). HRMS: 231.9914, calc. for $C_9H_{13}BrS$: 231.9921. MS: *m/z* (%) 232/234 (25, M^+), 217/219 (100), 138 (16), 123 (15).

3-Bromo-5-ethyl-2-isopropylthiophene 1,1-dioxide (**5**) was synthesized according to the literature.[3,4] The product was obtained when **4** (2.31 g, 9.91 mmol) was oxidized and chromatographed on a Chromatotron™ using gradient elution starting from heptane and ending with diethyl ether. The title compound 1.42 g (39%) was obtained as a clear oil. ^{1}H NMR: δ 6.26 (t, 1 H, H-4, *J*=2.1), 3.10 [septet, 1 H, C*H*$(CH_3)_2$, *J*=7.1], 2.50 (dq, 2 H, CH_2CH_3, *J*=7.0, 2.1 Hz), 1.39 [d, 6 H, CH(C*H*$_3)_2$, *J*=7.1], 1.24 (t, 3 H, CH_2C*H*$_3$, *J*=7.0). ^{13}C NMR: δ 146.37 (C-2), 143.39 (C-5), 125.12 (C-4), 119.37 (C-3), 28.88 [CH(*C*H$_3)_2$], 19.66 [*C*H$(CH_3)_2$], 17.09 (*C*H_2CH_3), 10.73 (CH_2*C*H_3). HRMS: 263.9819, calc. for $C_9H_{13}BrO_2S$: 263.9820. MS: *m/z* (%) 264/266 (35, M^+), 201 (35), 185 (63), 121 (100).

Synthesis of **6** *and* **7** *via ring-opening of* **5**.[1] L-Prolinol (1599.59 mg, 15.82 mmol) and **5** (798.16 mg, 3.01 mmol) were dissolved in *p*-xylene (24.0 ml) and placed with a condenser in an oil bath at 80 °C under argon. The reaction was complete after 5.25 h, as determined by TLC and GLC; the reaction mixture was diluted with diethyl ether and washed with water to remove the excess of L-prolinol. The ethereal phase was dried over magnesium sulfate and then evaporated *in vacuo* to give a crude product. The components were separated on a Chromatotron™ with heptane–ethyl acetate–triethylamine–methanol (90:10:5:1) as the eluent.

{(2S)-1-[(2R)(3E,5Z)-5-Bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1H-pyrrol-2-yl}methanol (**6**). Yield: 171.50 mg (19%) IR (film): ν 3406b (OH), 1634m (C=C stretch, conjug. diene), 1598m, 1456s, 1378s, 1300s, 1168s, 1118s, 1031s, 953s (CH bend, *trans*-RCH–CHR). ^{1}H NMR: δ 6.04 (d, 1 H, 5-H, *J*=14.9), 6.00 (dd, 1 H, 3-H *J*=14.9, 6.1), 5.69 (d, 1 H, 6-H *J*=8.8), 3.46 (dd, 1 H, 1″-CH_2 *J*=−10.6, 4.6), 3.34 (m, 1 H, 2-H, *J*=6.6, 6.1 Hz), 3.30 (dd, 1 H, 1″-CH_2 *J*=−10.6, 3.0), 2.94 (m, 2 H, 2′-H, 5′-H_{eq}), 2.81 (m, 1 H, 7-H, *J*=8.8, 6.7), 2.50 (1 H, 5′-H_{ax}), 1.87–1.60 (m, 4 H, 3′-, 4′-H_2), 1.15 (d, 3 H, 1-CH_3 *J*=6.8), 1.00 (d, 6 H, 8-CH_3, *J*=6.7). ^{13}C NMR: δ 140.51 (C-6), 136.88 (C-3), 129.31 (C-4), 122.43 (C-5), 63.94 (C-11″), 60.69 (C-2′), 58.11 (C-2), 50.34 (C-5′), 31.10 (C-7), 29.20 (C-3′), 24.52 (C-4′), 21.75 (C-8), 17.37 (C-1). HRMS: 302.1104, calc. for C14$H_2$5BrNO(M+H): 302.1119. MS: *m/z* (%) 302/304 [92, (*M*+H)+], 270/272 (45), 222 (95), 123 (100).

{(2S)-1-[(2S)(3E,5Z)-5-Bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1H-pyrrol-2-yl}methanol (**7**). Yield: 92.34 mg (10%). IR (film): ν 3406b (OH), 1634m (C=C stretch, conjug. diene), 1598m, 1456s, 1378s, 1300s, 1168s, 1118s, 1031s, 953s (CH bend, *trans*-RCH=CHR). ^{1}H NMR: δ 6.04 (d, 1 H, 4-H, *J*=14.9 Hz), 6.03 (dd, 1 H, 3-H, *J*=14.9, 3.4), 5.72 (d, 1 H, 6-H, *J*=8.8), 3.56 (dd, 1 H, 1′-H_2, *J*=−10.6, 4.1), 3.40 (m, 1 H, 1-H, *J*=6.8, 3.4), 3.34 (dd, 1 H, 1″-H_2, *J*=−10.6, 2.7), 2.98 (1 H, 5′-H_{eq}), 2.91 (m, 1 H, 2′-H, *J*=4.1, 2.7), 2.85 (m, 1 H, 7-H, *J*=8.8, 6.7), 2.63 (1 H, 5′-H_{ax}), 1.88–1.62 (m, 4 H, 3′-, 4′-H_2), 1.26 (d, 3 H, 1-CH_3, *J*=6.8), 1.06 (d, 6 H, 8-CH_3, *J*=6.7). ^{13}C NMR: δ 140.72 (C-6), 133.45 (C-3), 130.86 (C-4), 122.35 (C-5), 62.25 (C-1″), 60.20 (C-2′), 56.01 (C-2), 47.71 (C-5′), 31.13 (C-7), 28.52 (C-3′), 24.00 (C-4′), 21.76 (C-8), 20.86 (C-1). HRMS: 302.1098, calc. for $C_{14}H_{25}BrNO$ (*M*+H): 302.1119. MS: *m/z* (%) 302/304 [92, (*M*+H)$^+$], 270/272 (45), 222 (95), 123 (100).

Synthesis of **8** *and* **9** *via Swern oxidation and the Horner–Emmons reaction.*[6,7] Oxalyl chloride (104 ml, 1.21 mmol) was dissolved in dichloromethane (8.0 ml) at −60 °C under argon. Dimethyl sulfoxide (170 µl, 2.39 mmol) in dichloromethane (2.0 ml) was added dropwise via a syringe from an adjacent cold bath. A 65:35 mixture of **6** and **7** (1.00 mmol) in dichloromethane (6.0 ml) was injected 10 min later, after which the reaction mixture was stirred for 35 min before triethylamine (690 µl, 4.94 mmol) was added. After 40 min at −60 °C the reaction mixture was allowed to reach ambient temperature over 1 h. The solvent was evaporated off and the residue was washed twice with heptane and

once with ethyl acetate; these solutions were combined and then evaporated. Meanwhile, fresh phosphonate reagent was prepared: to a dispersion of sodium hydride (24.00 mg, 1.00 mmol) in tetrahydrofuran (2 ml) at 0 °C under an argon atmosphere was added triethyl phosphonoacetate (224.19 mg, 1.00 mmol) in tetrahydrofuran (1 ml). The triethyl phosphonoacetate was allowed to react for 1 h before the crude aldehyde, dissolved in anhydrous tetrahydrofuran (2 ml), was injected into the mixture, which then was allowed to reach ambient temperature. After 1.5 h the reaction was complete as determined by TLC. The mixture was washed with pH 7 buffer and water before it was dried over magnesium sulfate and finally evaporated *in vacuo*. Compounds **8** and **9** were obtained in a 65:35 ratio in 64% overall yield after separation on a Chromatotron™ with heptane–ethyl acetate–triethylamine (90:10:5) as the eluent.

(E)-Ethyl 3-{(2S)-1-[(2R and S)(3E,5Z)-5-bromo-7-methyl-3,5-octadien-2-yl]tetrahydro-1H-pyrrol-2-yl}-2-propenoate (**8** *and* **9**). Yield: 237.01 mg (64%). IR (film): ν 2869s, 1707s (C=O), 1648m (C=C stretch, conjug. diene), 1460m, 1369s, 1264s, 1154s, 958s (CH bend, *trans*-RCH=CHR). ^{1}H NMR: δ 6.84 (dd, 1 H, 3″-H, J=15.5, 8.0), 6.03 (d, 1 H, 4-H, J=14.8), 5.95 (dd, 1 H, 3-H, J=14.8), 5.85 (d, 1 H, 2″-H, J=15.5), 5.69 (d, 1 H, 6-H, J=8.5), 4.17 (q, 2 H, OCH_2, J=7.1), 3.36 (1 H, 2-H), 3.30 (1 H, 5′-H_2-eq), 2.96 (1 H, 2′-H, J=8.0), 2.84 (m, 1 H, 7-H, J=8.5, 6.7), 2.54 (1 H, 5′-H_2-ax), 2.00–1.60 (4 H, 3′-H_2, 4′-H_2), 1.28 (t, 3 H, OCH_2CH_3, J=7.1), 1.22 (d, 1 H, 1-H_3), 1.13 (d, 2 H, 1-H_3), 1.02 (d, 6 H, 8-H_3, J=6.7). ^{13}C NMR: δ 166.65, 151.77, 151.50, 140.60, 140.30, 137.31, 133.41, 130.84, 129.27, 122.54, 121.33, 120.83, 61.93, 61.75, 60.30, 60.20, 57.78, 56.03, 49.72, 47.05, 31.86, 31.53, 31.13, 31.09, 29.69, 23.11, 22.98, 21.76, 20.84, 17.29, 14.27. HRMS: 369.1304, calc. for $C_{18}H_{28}BrNO_2$ (M+H): 369.1303. HRMS: 369.1313, calc. for $C_{18}H_{28}BrNO_2$ (M+H): 369.1303.

Intramolecular Diels–Alder reaction. The diastereomeric mixture of **8** and **9** (225.67 mg, 0.6094 mmol) was dissolved in toluene (75 ml) in a 100 ml glass ampoule, which was repeatedly, i.e. three times, evacuated and flushed with argon before being sealed and placed in an oil bath at 100 °C. Samples for ^{1}H NMR samples were taken in order to monitor the progress of the IMDA. The minor triene was consumed quantitatively after 14 h at 100 °C; the temperature was raised to 120 °C and the reaction continued for another 33 h before the major triene was consumed quantitatively too.

Separation of the IMDA isomers was achieved after HPLC chromatography using a mixture of ethyl acetate–pentane–isopropyl alcohol–triethylamine (60:20:15:5) as the eluent. The four components were isolated in a total yield of 216.75 mg (96%). The diastereomer **8** (146.69 mg, 0.3961 mmol) gave 140.82 mg (96%) of **10** and **11** in a ratio of 86:14 and the diastereomer **9** (78.98 mg, 0.2687 mmol) gave 75.82 mg (96%) of **12** and **13** in a ratio of 90:10.

(5R,5aS,8R,9R,9aS,9bS)-Ethyl 7-Bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1H-pyrrolo[2,1-a]-isoindole-9-carboxylate (**10**). $[\alpha]_D$ 60.4 (*c* 1.294, $CHCl_3$). IR (film): ν 1726s (C=O). ^{1}H NMR: δ 6.06 (1 H, 6-H), 4.09 (q, 2 H, OCH_2, J=7.2), 3.97 (1 H, 5-H, J=7.2), 3.93 (m, 1 H, 9b-H, J=11.4), 3.24 (1 H, 3-H_2-eq), 3.06 (m, 1 H, 5a-H, J=11.4, 7.2), 3.01 (dd, 1 H, 9-H, J=11.4, 6.6), 2.95 (1 H, 8-H, J=6.6), 2.89 (1 H, 3-H_2-ax), 2.38 (1 H, 1-H_2-eq), 2.18 (q, 1 H, 9a-H, J=11.4), 2.08 (2 H, 2-H_2), 1.94 (1 H, 1-H_2-ax), 1.91 (m, 1 H, 10-H, J=7.1), 1.24 (t, 3 H, OCH_2CH_3, J=7.2), 1.12 (d, 3 H, 10-H_3, J=7.1), 1.11 (d, 3 H, 5-H_3, J=7.2), 1.02 (d, 3 H, 10-H_3, J=7.1). ^{13}C NMR: δ 172.12 (C-H), 127.05 (C-6), 126.60 (C-7), 70.97 (C-9b), 61.34 (OCH_2), 57.38 (C-5), 52.32 (C-5a), 51.15 (C-8), 50.51 (C-9), 46.26 (C-3), 39.82 (C-9a), 32.31 (C-H), 30.27 (C-10), 28.87 (C-2), 24.13 (10-CH_3), 20.63 (10-CH_3), 14.50 (OCH_2CH_3), 12.47 (5-CH_3). HRMS: 369.1296, calc. for $C_{18}H_{28}BrNO_2$ (M+H): 369.1303.

(5R,5aR,8S,9S,9aR,9bS)-Ethyl 7-Bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1H-pyrrolo[2,1-a]-isoindole-9-carboxylate (**11**). IR (film): ν 1726s (C=O). ^{1}H NMR: δ 6.14 (d, 1 H, 6-H, J=2.0), 4.43 (m, 1 H, 9b-H, J=8.0), 4.18 (q, 2 H, OCH_2, J=7.2), 3.45 (1 H, 3-H_2-eq), 3.35 (m, 1 H, 5-H, J=12.0, 7.2), 3.02 (br d, 1 H, 8-H, J=5.6), 2.90 (dd, 1 H, 9-H, J=12.0, 5.6), 2.67 (1 H, 3-H_2-ax), 2.40 (dt, 1 H, 9a-H, J=12.0, 8.0), 1.94 (2 H, 2-H_2), 2.02 (m, 1 H, 5a-H, J=12.0, 2.0), 1.92 (1 H, 1-H_2-eq), 1.87 (m, 1 H, 10-H, J=7.1), 1.30 (t, 3 H, OCH_2CH_3, J=7.2), 1.16 (d, 3 H, 10-H_3, J=7.1), 1.38 (d, 3 H, 5-H_3, J=7.2), 1.08 (d, 3 H, 10-H_3, J=7.1). ^{13}C NMR: δ 171.78 (C-11), 127.27 (C-6), 126.46 (C-7), 66.68 (C-9b), 61.52 (OCH_2), 60.28 (C-5), 47.11 (C-5a), 51.68 (C-8), 48.45 (C-9), 48.10 (C-3), 39.16 (C-9a), 26.73 (C-1), 30.47 (C-10), 25.80 (C-2), 24.62 (10-CH_3), 20.74 (10-CH_3), 14.58 (OCH_2CH_3), 12.91 (5-CH_3). HRMS: 369.1304, calc. for $C_{18}H_{28}BrNO_2$ (M+H): 369.1303.

(5S,5aS,8R,9R,9aS,9bS)-Ethyl 7-Bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1H-pyrrolo[2,1-a]-isoindole-9-carboxylate (**12**). $[\alpha]_D$ 35.5 (*c* 0.664, $CHCl_3$). IR (film): ν 1726s (C=O). ^{1}H NMR: δ 6.17 (1 H, 6-H), 4.13 (q, 2 H, OCH_2, J=7.2), 3.48 (1 H, 9b-H), 3.10 (1 H, 3-H_2-eq), 2.96 (1 H, 9-H, J=11.3), 2.93 (1 H, 8-H), 2.57 (1 H, 3-H_2-ax), 2.45 (dd, 1 H, 5-H, J=11.3, 6.0), 2.27 (t, 1 H, 5a-H, J=11.3), 2.11 (1 H, 1-H_2-eq), 1.97 (m, 1 H, 10-H, J=7.1), 1.93 (1 H, 1-H_2-ax), 1.92 (2 H, 2-H_2), 1.86 (t, 1 H, 9a-H, J=11.3), 1.28 (t, 3 H, OCH_2CH_3, J=7.2), 1.24 (d, 3 H, 5-H_3, J=6.0), 1.13 (d, 3 H, 10-H_3, J=7.1), 1.05 (d, 3 H, 10-H_3, J=7.1). ^{13}C NMR: δ 172.64 (C-11), 129.10 (C-6), 125.65 (C-7), 67.93 (C-9b), 64.29 (C-5), 60.91 (OCH_2), 55.52 (C-5a), 52.90 (C-3), 51.65 (C-8), 51.01 (C-9), 44.70 (C-9a), 33.11 (C-1), 30.33 (C-10), 27.76 (C-2), 24.08 (10-CH_3), 20.80 (10-CH_3), 17.97 (5-CH_3), 14.52 (OCH_2CH_3). HRMS: 369.1298, calc. for $C_{18}H_{28}BrNO_2$: 369.1303.

(5S,5aR,8S,9R,9aS,9bS)-Ethyl 7-Bromo-8-isopropyl-5-methyl-2,3,5,5a,8,9,9a,9b-octahydro-1H-pyrrolo[2,1-a]-isoindole-9-carboxylate (**13**). IR (film): ν 1726s (C=O). ^{1}H NMR: δ 6.13 (dd, 1 H, 6-H, J=5.9), 4.20 (q, 2 H, OCH_2, J=7.2), 3.99 (1 H, 9b-H), 3.34 (1 H, 3-H_2-eq), 3.31 (dd, 1 H, 5-H, J=6.6, 5.9), 2.86 (m, 1 H, 8-H, J=9.5), 2.73 (1 H, 3-H_2-ax), 2.66 (t, 1 H, H9, J=12.1), 2.56 (m, 1 H, 10-H, J=7.1), 2.44 (m, 1 H, 5a-H, J=7.3, 5.9), 2.25 (1 H, 1-H_2-eq), 2.18 (m, 1 H, 9a-H, J=12.1, 7.3), 1.96 (2 H, 2-H_2), 1.49 (1 H, 1-H_2-ax), 1.36 (d, 3 H, 5-H_3, J=6.6), 1.30 (t, 3 H, OCH_2CH_3, J=7.2), 0.93 (d, 3 H, 10-H_3, J=7.1), 0.84 (d, 3 H, 10-H_3, J=7.1). ^{13}C NMR: δ 175.29 (C-11), 131.93 (C-7), 125.82 (C-6), 67.88 (C-9b), 61.80 (OCH_2), 61.30 (C-5), 48.43 (C-8), 47.50 (C-3), 46.28 (C-9a), 44.44 (C-5a), 43.67 (C-9), 33.24 (C-1), 30.68 (C-10), 26.06 (C-2), 20.06 (10-CH_3), 16.23 (10-CH_3), 14.60 (OCH_2CH_3), 13.72 (5-CH_3). HRMS: 369.1301, calc. for $C_{18}H_{28}BrNO_2$ (M+H): 369.1303.

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References

1. Tsirk, A., Gronowitz, S. and Hörnfeldt, A.-B. *To be published.*
2. Karlsson, J. O., Gronowitz, S. and Hallberg, A. *Chem. Scr. 20* (1982) 37.
3. van Tilborg, W. J. M. *Synth. Commun.* (1976) 583.
4. Tsirk, A., Gronowitz, S. and Hörnfeldt, A.-B. *Tetrahedron 51* (1995) 7035.
5. Professor Jan Sandström. *Personal communication.*
6. Ireland, R. E. and Norbeck, D. W. *J. Org. Chem. 50* (1985) 2198.
7. Kametani, T., Higashiyama, K. Otomatsu, H. and Honda, T. *Isr. J. Chem. 27* (1986) 57.
8. Whitesell, J. K., LaCour, T., Lovell, R. L., Pojman, J., Ryan, P. and Yamada-Nosaka, A. *J. Am. Chem. Soc. 110* (1988) 991.
9. Tsirk, A., Gronowitz, S. and Hörnfeldt, A.-B. *Helv. Chim. Acta* (1997). *In press.*
10. McGregor, S. D. and Lemal, D. M. *J. Am. Chem. Soc. 88* (1966) 2858.
11. Mock, W. L. *J. Am. Chem. Soc. 97* (1975) 3673.
12. Gronowitz, S., Hallberg, A. and Nikitidis, G. *Tetrahedron 43* (1987) 4793.
13. Gronowitz, S., Hörnfeldt, A.-B., Lukevics, E. and Pudova, O. *Synthesis* (1994) 40.
14. Tsirk, A., Gronowitz, S. and Hörnfeldt, A.-B. *Tetrahedron 53* (1997) 771.
15. McDowell, S. T. and Stirling, C. J. M. *J. Chem. Soc. B* (1967) 343.
16. McDowell, S. T. and Stirling, C. J. M. *J. Chem. Soc.* (1967) 349.
17. McDowell, S. T. and Stirling, C. J. M. *J. Chem. Soc.* (1967) 351.
18. Houk, K. N., Paddon-Row, M. N., Rondan, N. G., Wu, Y.-D., Brown, F. K., Spellmayer, D. C., Metz, J. T., Li, Y. and Loncharich, R. J. *Science 231* (1986) 1108.
19. Rudolf, K., Hawkins, J. M., Loncharich, R. J. and Houk, K. N. *J. Org. Chem. 53* (1988) 3879.
20. Osman, R., Namboodiri, K., Weinstein, H. and Rabinowitz, J. R. *J. Am. Chem. Soc. 110* (1988) 1701.
21. SPARTAN version 4.0, Wavefunction Inc., Von Karman, Suite 370, Irvine, California 92715, USA.
22. Morokuma, K. *Acc. Chem. Res.* (1977) 294.

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