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Formation of Substituted Benzo[*a*]heptalenes *via* Bergman Cyclization of Vicinal Di(ethynyl)-heptalenes

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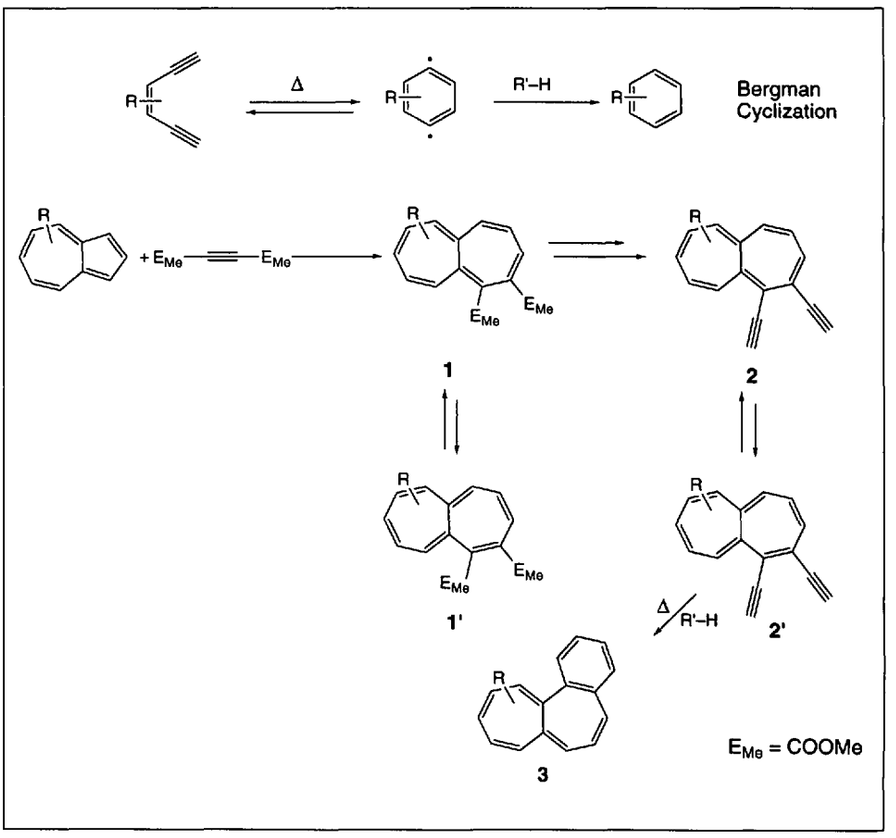
Abstract. By Hafner's synthesis, dimethyl heptalene-4,5-dicarboxylates are easily available from azulenes and dimethyl acetylene-dicarboxylate. Treatment with Takai reagent leads to 4-acetylheptalene-5-carboxylates, which by the procedure of Negishi *et al.* are further transformed into 4-ethynyl-heptalene-5-carboxylates. Reduction to heptalene-5-methanols, followed by Swern oxidation yields the corresponding heptalene-5-carbaldehydes. Treatment with trimethylsilyldiazomethane in the presence of butyllithium gives 4,5-di(ethynyl)-heptalenes, which on heating in chlorobenzene in the presence of cyclohexa-1,4-diene are transformed into benzo[a]heptalenes.

Keywords: Benzo[a]heptalenes · Bergman cyclization · Colchicines · Corey procedure · Negishi procedure · Ohira procedure · Takai reagent

Benzo[*a*]heptalenes, the underlying structure of naturally occurring colchicines, have been synthesized by degradation of the latter compounds [1], by application of Hafner's heptalene synthesis [2] to benz[*a*]azulenes and dimethyl acetylene-dicarboxylates [3][4] or by reaction of vicinal heptalen-dicarboxylates and derivatives of them with an excess of lithiated methyl sulfones as C_1 source and butyllithium [5]. The latter procedure starts already with heptalene precursors, which carry 14 of the necessary 16 C-atoms of the benzo[*a*]heptalene skeleton, ready to be further transformed into colchicinoids (*cf.* [5c]). One of the most exciting benzene-ring forming reactions, having a great biological relevance and potential [6], is without doubt the Bergman cyclization of ene-diynes [7], which may also be useful for the synthesis of benzo[*a*]heptalenes, starting with heptalene-dicarboxylates. This requires the



Scheme 1.

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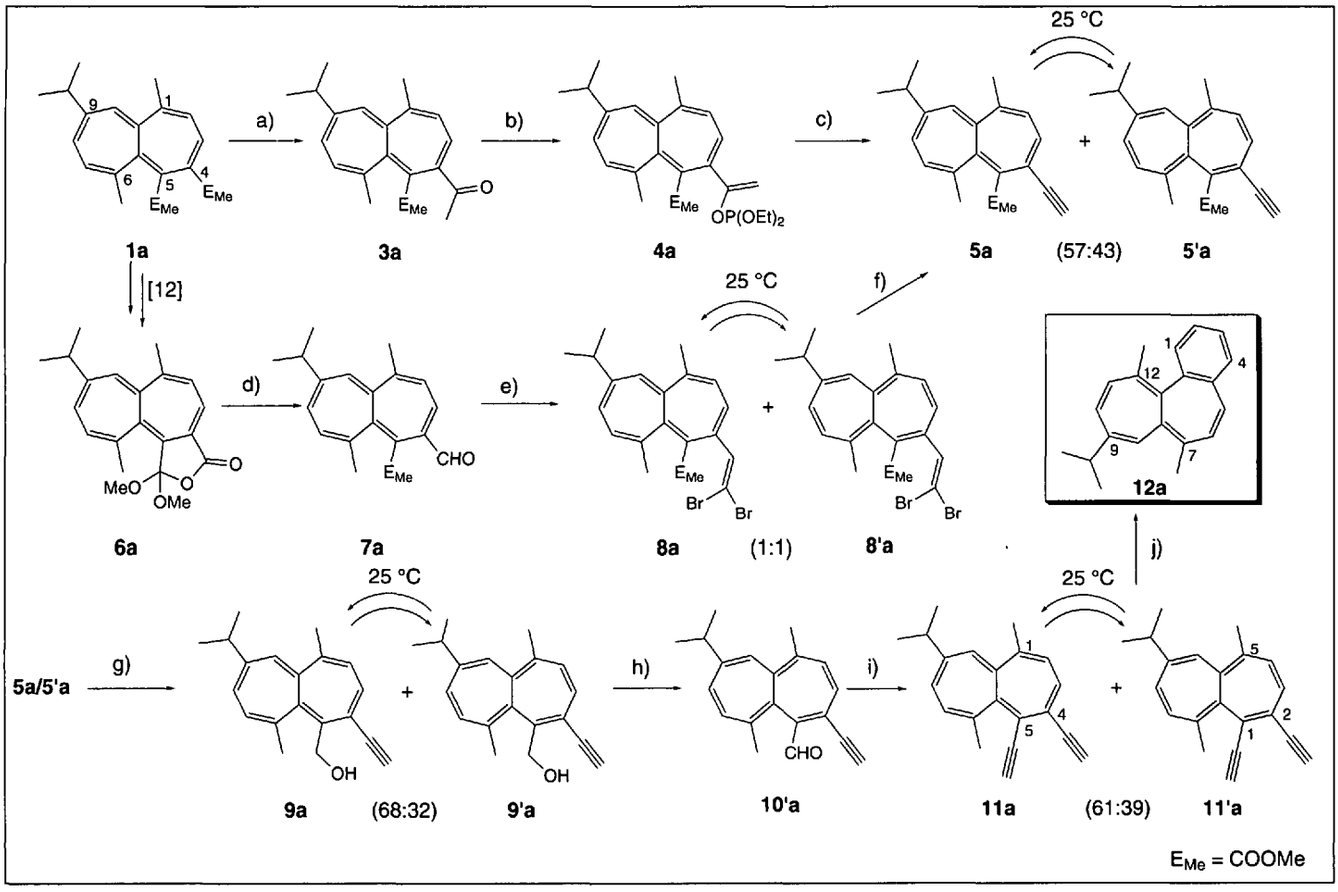
two ester functions of vicinal heptalene-dicarboxylates **1** or their double-bond shifted (DBS) isomers **1'**, which readily convert thermally or photochemically into each other (*cf.* [8]), to be transformed into ethynyl groups (Scheme 1).

Dimethyl 9-isopropyl-1,6-dimethyl-heptalene-4,5-dicarboxylate (**1a**) [5a][9] was chosen as a model compound to test the proposed procedure (Scheme 2). When **1a** was reacted in THF with 2.6 mol-equiv. of freshly prepared Takai reagent [10] at r.t., a selective methylenation at MeOCO–C(4) took place, and, after hydrolysis, the 4-acetylheptalene-5-carboxylate **3a** (m.p. 121–122 °C) was obtained in 66% yield. The 'one-pot' protocol of Negishi *et al.* [11] was tested for the transformation of **3a** to **5**. However, the intermediate diethyl phosphate **4a** was isolated instead and purified by flash chromatography on silica gel (Et_2O/hexane 4:1). In the elimination reaction of **4a**, at –78 °C instead of at –78 °C to r.t., LDA (lithium di(isopropyl)amide) was substituted by LTMP (lithium 2,2,6,6-tetramethylpiperidide). These modifications gave much better results, the expected ethynylheptalene-carboxylate was obtained as a mixture of both double bond shift (DBS) isomers **5a/5'a** (95% with respect to **3a**, 63% with respect to **1a**). Both isomers, **5a** and **5'a**, could easily be distinguished by ^{1}H NMR ($CDCl_3$), which *e.g.* for the signal of the H-atom of the ethynyl group exhibited two *s* at 2.98 (**5a**) and 3.47 ppm (**5'a**) (57:43), representing the equilibrium ratio of **5a** and **5'a** at r.t. Another approach to **5a/5'a** started with the pseudo-ester **6a** of **1a**, available from **1a** in two steps [12] (see also [5c]). It was reduced with DIBAH in toluene at –90 °C to the corresponding 4-formylheptalene-5-carboxylate **7a** (*cf.* [9]). For the transformation **7a** → **5a/5'a**, the method of Corey and Fuchs [13] was applied. Reaction of **7a** with CBr_4/PPh_3 in CH_2Cl_2 gave the crystalline 4-(2,2-dibromoethenyl)-heptalene-5-carboxylates **8a/8'a** (90%). A thermodynamically controlled 1:1 mixture **8a/8'a** was rapidly established in the NMR ($CDCl_3$): a sharp *s* at 7.63 ppm and a comparably broad *s* at 7.13 ppm for the H-atom of the dibromo-ethynyl group of **8'a** and **8a** respectively, were observed. Treatment of **8a/8'a** with 3 mol-equiv. of LDA at –78 °C/10 min gave 89% of **5a/5'a**. A slightly lower yield (77%) was realized with BuLi as base. The yield of **5a/5'a** with respect to **6a** amounted to 69–76%; however, with respect to **1a** the yield was 50–55%.

Reduction of **5a/5'a** with DIBAH in toluene at –90 °C gave 95% yield of the ethynylheptalene-methanol, a mixture of the two DBS isomers **9a/9'a** (68:32). Reduction of **5a/5'a** protected by a trimethylsilyl ethynyl group was much less successful and delivered **9a/9'a** in ≤ 28%. The ^{1}H NMR spectrum ($CDCl_3$) of **9a/9'a** showed the two *s* of the H-atom of the ethynyl groups at 3.14 (**9a**) and 3.27 ppm (**9'a**) and two *t* for the H-atom of the OH groups at 1.94 (**9'a**) and 1.78 ppm (**9a**). Swern oxidation of **9a/9'a** gave 71% of the corresponding 2-ethynylheptalene-1-carbaldehyde **10'a** (^{1}H NMR ($CDCl_3$): CHO, *s* at 10.16 ppm and ≡CH, *s* at 3.51 ppm). No signals for the DBS isomer **10a** could be observed. The last step, *i.e.*,

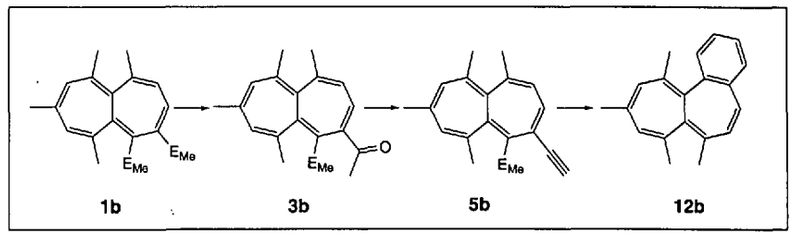


Scheme 2. a) 1. 2.6 Mol-equiv. Takai reagent/THF, Ar, r.t./4 h; 2. 0.5 conc. HCl, r.t./15 min, 66%. b) 1. 2.1 Mol-equiv. LDA/THF, Ar, –78 °C/1 h; 2. 2.1 mol-equiv. $ClOP(OEt)_2$, –78 °C/4 h, 99%. c)7 Mol-equiv. LTMP/THF, Ar, –78 °C/3 h, 95% **5a/5'a** (57:43). d) 1 Mol-equiv. DIBAH/toluene, –90 °C/1 h, 91%. e) 3 Mol-equiv. PPh_3, 1.5 mol-equiv. CBr_4/CH_2Cl_2, 0 °C → r.t./1 h, 90 %, **8a/8'a** (1:1). f) 3 Mol-equiv. LDA/THF, Ar, –78 °C/10 min, 89% **5a/5'a** (57:43). g) 2 Mol-equiv. DIBAH/toluene, Ar, –90 °C/0.5 h, 95% **9a/9'a** (68:32). h) Swern oxd./CH_2Cl_2, Ar, –60 °C → 0 °C/1.5 h, 71%. i) 2 Mol-equiv. $(CH_3)_3Si$-$CLiN_2$/THF, Ar, –78 °C/1 h, then 0 °C/1h, 48% **11a/11'a** (61:39). j) 20 Mol-equiv. cyclohexa-1,4-diene/chlorobenzene, Ar, 190 °C/2 h, ≥ 30%.

transformation of the carbaldehyde group of **10'a** into the second ethynyl group, was realized with trimethylsilyldiazomethane in the presence of BuLi, following the protocol of Ohira *et al.* [14], yielding 48% of the di(ethynyl)heptalene again as a thermodynamically controlled mixture of the two DBS isomers **11a/11'a** (61:39). Their structures could be unequivocally assigned by NMR ($CDCl_3$; **11a**: C(4)–C≡C–H, slightly broadened *s* at 3.12 ppm; C(5)–C≡C–H, *s* at 3.24 ppm; **11'a**: C(2)–C≡C–H, *s* at 2.95 ppm; C(1)–C≡C–H: *s* at 3.32 ppm).

The thermal conversion of **11a/11'a** into benzo[*a*]heptalene **12a** was performed in chlorobenzene in the presence of a 20-fold molar excess of cyclohexa-1,4-diene at 190 °C/2 h (*cf.* [15]). The yield (≥ 30%) was difficult to determine, **12a** turned out to be quite unstable. Nevertheless, its UV/VIS spectrum (hexane) (see Fig.) is very similar to that of benzo[*a*]heptalene itself, whose *extrema* [3c] are given in parentheses (for further derivatives see [1]): λ_{max} at 325 (347), 256 (259) and 213 (*ca.* 202) nm and a shoulder at 280 (295) nm. The bathochromic shift of the heptalene band I (*cf.* [16]) by 22 nm is in agreement with larger torsion angles at the central σ-bond of **12a** due to the *peri*-standing Me groups. The ^{1}H NMR spectrum ($CDCl_3$) of **12a** showed the expected signals: 7.39–7.28 (*m*, H–C(1, 2, 3)); 7.01 (*d*, *J* = 7.1, H–C(4)); 6.84 (*d*, *J* = 11.7, H–C(5)); 6.44 (*d*, *J* = 11.9, H–C(11)); 6.37 (*d*, *J* = 12.2, H–C(10)); 6.25 (*d*, *J* = 11.8, H–C(6)); 5.70 (br. *s*, H–C(8)); 2.55 (sept., Me_2CH–C(9)); 1.72 (*s*, Me–C(7)); 1.62 (*s*, Me–C(12)); 1.16/1.15 (2 d, J = 6.9/6.9, Me_2CH–C(9)). In the same manner dimethyl 1,6,8,10-tetramethyl-heptalene-4,5-dicarboxylate (**1b**) was transformed *via* the corresponding 4-acetyl- and 4-ethynylheptalene-5-carboxylates **3b** (m.p. 129–131 °C) and **5b**, respectively, into benzo[*a*]heptalene **12b** (Scheme 3).

The described procedures demonstrate that the Bergman cyclization is indeed suitable for the construction of the benzo[*a*]heptalene skeleton, starting with heptalene-dicarboxylates. However, the procedures need still a number of improvements to be applicable for the synthesis of new colchicinoids with modified biological activities as compared with those of colchicine (*cf.* [17]).



Scheme 3. Reaction conditions as in Scheme 2.

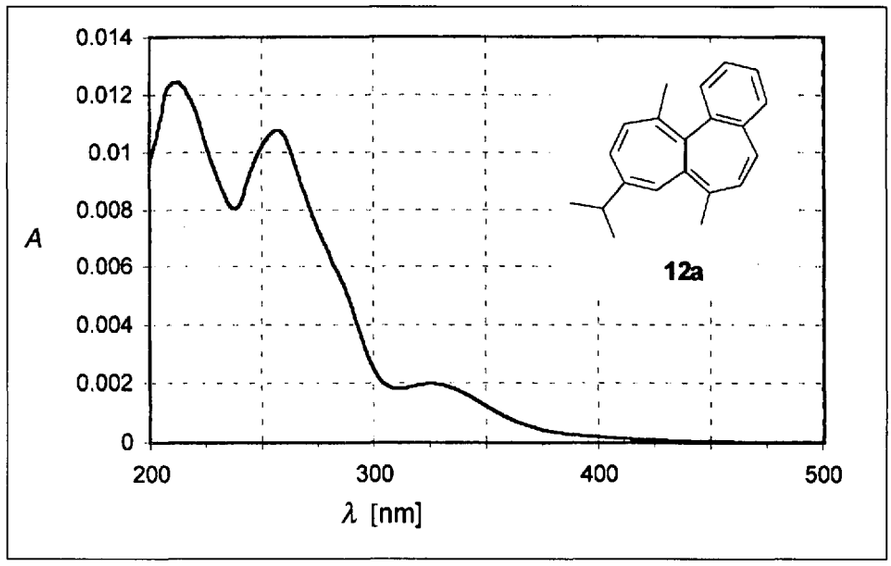


Fig. UV/VIS spectrum of **12a**

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