The Diels–Alder Reaction of 3-Acetoxy-1-vinylcyclohexene with Methyl Vinyl Ketone

Takeshi KAWAMATA,*[,a] Kenzo HARIMAYA,[a] Yoichi IITAKA,[b] and Seiichi INAYAMA[a]

Pharmaceutical Institute, School of Medicine, Keio University,[a] 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan, and University of Tokyo,[b] 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. *Received December 12, 1988*

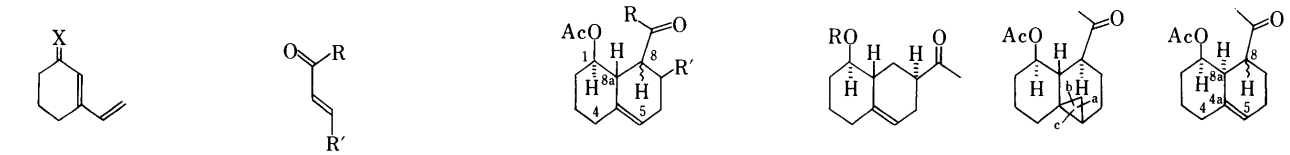
The Diels–Alder reaction of 3-acetoxy-1-vinylcyclohexene (1c) with methyl vinyl ketone (MVK) at 110 and 150 °C gave predominantly the adducts 1-acetoxy-8-acetyl-8aβH-4a(5)-octalin, 3b (8βH) and 3a (8αH), respectively, along with other minor adducts. The stereochemistry of 3a was independently confirmed by X-ray crystallographic analysis of the *p*-bromobenzoate (3e) derived from 1-desacetyl-3a(3d). The predominant approach of the dienophile (MVK) to 1c was found to have occurred *anti* to the allylic acetate group, contrary to the empirical rule proposed recently.

Keywords Diels–Alder reaction; 3-acetoxy-1-vinylcyclohexene; 1-acetoxy-8-acetyl-8aβH-4a(5)-octalin; temperature dependence; X-ray crystallography; *endo*-selectivity; face-selectivity; *anti*-addition

In the course of our continuing work on the application of 3-vinylcyclohex-2-en-one (**1a**) for the syntheses of relatively simple natural products, we have studied the Diels–Alder reaction of 3-acetoxy-1-vinylcyclohexene (**1c**) with methyl vinyl ketone (MVK) (**2a**) (R=CH_3, R′=H) for the following reasons.[1] First, the strategy of using a site-selective cyclopropane cleavage as an entry to functionalized *trans*- or *cis*-fused angularly methylated decalins is relatively unexplored. Hence, it was of interest to prepare the cyclopropyl derivative (**5**) *via* 1-acetoxy-8-acetyl-8aβH-4a(5)-octalin (**3**) and to investigate the site-selectivity of the cyclopropane cleavage of **5**; it was anticipated that the product obtainable by the rupture of the "a" bond between C(5) and C(5a) should provide an advanced precursor for the synthesis of non-isoprenoid sesquiterpene, β-gorgonene.[2] Second, it was expected that the Diels–Alder adduct (**3c**), accessible from **2c** (R=OR*, R=CH_3; R*=chiral auxiliary) and **1c**, would be easily transformable to the optically active hexahydronaphthalene portion of the well-known hypocholesterolemic agent compactin.[3] Third, to study the Diels–Alder reaction between the diene **1c** and **2a** itself seemed especially of interest, since the influence of an allylic asymmetric center on the π-facial course of the Diels–Alder reaction has recently been of great concern.[4] Battiste *et al.*[5] have reported an intermolecular Diels–Alder reaction of **1b** and **1d** with ethyl acrylate based on almost the same line as ours. However, they made no mention of the stereochemistries and the ratios of the cycloadducts involved. Moreover, the product ratio of the reaction between **1b** and MVK described by them seems different from ours. Perhaps this reflects the difference due to the C(1) oxygen substituent, such as hydroxyl or acetoxy.

We have studied the title reaction in detail and determined the relative stereostructures and ratios of all the cycloadducts produced. An interesting finding was made concerning the face-selectivity of the reaction. Herein, we wish to present our results on the stereochemical assignments of all the cycloadducts obtained and the selectivities of the title reaction.

Heating of **1c**,[6] derived from **1a** by lithium aluminum hydride reduction followed by acetylation (Ac_2O–pyridine), with MVK in a sealed tube at 150 °C for 48 h gave a mixture of stereoisomers of 1-acetoxy-8-acetyl-8aβH-4a(5)-octalin, from which a major fraction *Rf* 0.38 (**3a**+**4a**) (56%) and a minor one (**6b**) (9%) *Rf* 0.41, $C_{14}H_{20}O_3$. Chemical ionization mass spectrum (CI-MS) *m/z*: 237 (MH^+), and **6a** (5%) *Rf* 0.31, $C_{14}H_{20}O_3$, CI-MS *m/z*: 237 (MH^+) were separated by chromatography on silica gel. The major fraction, which was homogeneous by thin layer chromatography (TLC) (ether–hexane=1:1), was shown to be a mixture of isomers by examination of its ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum. The ratio was estimated to be 3:1 by the integration of the signals of diagnostic methyl groups (–$OCOCH_3$ and –$COCH_3$). Although separation at this stage was unsuccessful, hydrolysis with 5% KOH–dioxane followed by chromatography on silica gel provided the corresponding hydroxyketone (**3d**), $C_{12}H_{18}O_2$, mp 99—100 °C. IR ν_{max}^{KBr} cm^{-1}: 3480, 3305(sh), 1707, 1671, 1051, 1041, and its isomer (**4b**), $C_{12}H_{18}O_2$ in a ratio of 3:1, which was consistent with the ratio estimated from ^{1}H-NMR mentioned above. Acetylation of **3d** in the usual manner (Ac_2O–pyridine) afforded the corresponding acetate (**3a**), mp 55—56 °C. IR ν_{max}^{KBr} cm^{-1}: 1731, 1710, 1699 (w), 1253, whose NMR



1a : X=O
1b : X=<OH, H
1c : X=<OAc, H
[**1d** : X=<OSi≮, H]

2a : R=CH_3, R′=H
2b : R=R′=CH_3
[**2c** : R=OR*, R′=CH_3]

3a : R=CH_3, R′=H(8αH)
3b : R=CH_3, R′=H(8βH)
[**3c** : R′=CH_3, R=OR*]
3d : **3a**[C(1)-OH]
3e : **3a**[C(1)-$OCOC_6H_4Br(p)$]

4a : R=Ac
4b : R=H

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6a (8αH)
6b (8βH)

Chart 1

spectrum was found to be identical with that of the main adduct in the original fraction. Similarly, acetylation of **4b** gave the corresponding acetate (**4a**) contained in the major fraction. The experiments demonstrated that **3a** and **4a** had not suffered any structural changes, especially configurational changes at the C(8) and C(7) side chains, respectively, during their hydrolysis.

First, the structure of **3a** was deduced as follows. In the ^{1}H-NMR spectrum of **3a**, a 1H signal assignable to C(1)-H appeared at δ 4.42 with two large and one smaller coupling constants (J = 10.5, 10.5, 4.2 Hz). This suggested that C(1)-H and (8a)-H should be *trans*-diaxial relationship. Irradiation at δ 2.48 (1H, ddd, J = 11, 8, 3), ascribable to the methine proton on the carbon carrying the $-COCH_3$ substituent, changed the 1H methine triplet at 2.70 to a doublet, while the irradiation of the latter changed the former to double doublets. This indicated that this group should be located at C(8). Thus, the structure of **3a** including the stereochemical relationship between C(1)-H, C(8a)-H and C(8)-H (*trans*/*trans*) was deduced to be as illustrated in Chart 1. However, since the structure of **3a** was not consistent with Alder's rule, the reaction was carried out under milder conditions. Heating of **1c** with MVK at 110 °C for 24 h yielded the above-mentioned two chromatographically separable portions: *Rf* 0.38 (63%) and *Rf* 0.31 (17%). The major fraction contained a new isomer (**3b**), as expected, along with **3a** and **4a** in a ratio of 39 : 7 : 19 based on examination of its ^{1}H-NMR spectrum.[7] Hydrolysis of this material with 5% KOH–MeOH yielded the aforementioned **3d** and **4b** (*vide infra*) in a ratio of approximately 4 : 1, whereby demonstrating that the C(8)-side chain ($-COCH_3$) of the isomer (**3b**) had epimerized during the course of hydrolysis to afford the same hydrolysate **3d** as that derived from **3a**. This result suggested that the major adduct (**3b**) at 110 °C was an *endo*-type adduct and the one (**3a**) at 150 °C was an *exo*-type adduct as assigned above.

An unambiguous and direct structural proof of the acetate (**3a**) was obtained by X-ray crystallographic analysis of the *p*-bromobenzoate (**3e**), mp 131—133 °C, $C_{19}H_{21}BrO_3$, prepared from the corresponding ketol (**3d**) by the standard method. Figure 1 shows the crystal structure of **3e**. The ^{1}H-NMR spectrum of **3e** exhibited the same coupling constants as that of **3a** with respect to C(1)-H, C(8a)-H and C(8)-H. Hence, it follows that **3a** has the same stereostructure as that of **3e**. Thus, the structures of the more stable isomer (**3a**) and the epimer (**3b**) deduced chemically and spectrochemically were confirmed.

The structure of the minor isomers (**6a** and **6b**) were elucidated as follows. In the two-dimensional shift correlation spectrum of **6b**, cross peaks were observed between the 1H signal at δ 5.06 (br s) assignable to C(1)-H and the methine signal at δ 2.77 (1H, br) and in turn, between the latter and the signal at δ 2.58 (1H, ddd, J = 10.5, 10.5, 4 Hz). These data indicated that the methyl ketone group ($-COCH_3$) should be located at the C(8) position. Furthermore, the relative stereostructure of **6b** illustrated in Chart 1 was assigned from the coupling constants at C(1)-H, C(8a)-H and C(8)-H as well as a consideration of its Dreiding model. It is interesting that the coupling patterns at C(1)-H and C(8a)-H supported an axial disposition of the ester group ($OCOCH_3$) at C(1). The structure of **6a** was elucidated as shown since it changed to **6b** on a brief exposure to base (K_2CO_3). Therefore, the fifth isomer (**4a**) should necessarily be the regioisomer of **3**, and its relative stereostructure was inferred to be as shown on the basis of its ^{1}H-NMR spectrum (C(1)-H; ddd, C(7)-H; ddd). Thus, the stereostructures of all the cycloadducts were established.

In conclusion, as regards the *endo*- and *exo*-selectivity of the cycloaddition products of the title reaction at 110 °C, not only the major product **3b** but also the *syn* type product **6a** and even the regioisomer **4a** were found to be *endo* in accord with the general preference for *endo* orientation predicted by Alder's rule. However, interestingly, the predominant product **3b** and hence **3a** were *anti* adducts; this appears to be contrary to the rule proposed recently.[4] This presumably arises because the directing allylic acetoxyl group of the diene can not sufficiently participate in the transition state to form the *syn* adduct since it is situated on the cyclohexane ring. This assumption seems to be collaborated by the result that the regioisomer **4a** was the *anti* adduct; this means that the carbonyl group of the dienophile and the acetoxyl group of the diene are far apart in the transition state so that a much smaller directing effect of the latter operates as compared to the case of formation of **3**.

Finally, it is noteworthy that the introduction of the methyl group at C(4a) of **3** *via* cyclopropane formation and selective cleavage was successfully achieved [8] and **3** should be useful as an advanced precursor of natural products such as β-gorgonene and compactin.

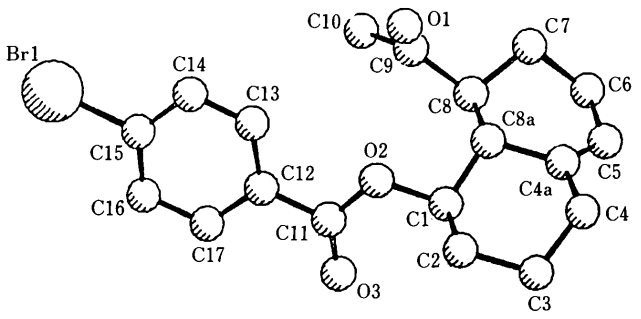

Fig. 1. The Perspective View of *p*-Bromobenzoate (**3e**)

Experimental

Melting points were determined on Büchi melting point apparatus. Infrared (IR) spectra were recorded on a Hitachi EPI-G3 spectrophotometer. Mass spectra were taken on a JEOL JMS-D300 instrument (JMA-200 data analysis system). ^{1}H-NMR spectra (200 MHz) were recorded with Varian XL-200 with tetramethylsilane as an internal standard. TLC was performed on a Kiesel gel 60 F_{254} plate (Merck) using ether–hexane (gradient).

Preparation of 1c A solution of **1a** (150 mg) in dry ether (1 ml) was added to a stirred suspension of $LiAlH_4$ (32 mg) in dry ether (7 ml) at −15 °C, and the mixture was stirred for 1.5 h, then acidified with dilute HCl, and extracted with ether. The extract was dried over $MgSO_4$. Evaporation of the solvent left a viscous oil, which was dissolved in pyridine (0.5 ml) and Ac_2O (0.5 ml). The solution was stirred at room temperature for 2 d, poured into dilute HCl, and extracted with ether. The extract was dried over $MgSO_4$. Evaporation of the solvent followed by purification by chromatography on silica gel with hexane–ether provided 147 mg of **1c** (73%). IR ν_{max}^{KBr} cm^{-1}: 1741, 1609, 1242, 913. $C_{10}H_{14}O_2$ (M_r 166). EI-MS *m/z*: 106 ($M^+ - 60$). High-resolution MS *m/z*: 106.0788 (Calcd for C_8H_8: 106.0782). ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.21 (6H, m), 2.06 (3H, s), 5.08 (1H, d, J = 10.6 Hz), 5.25 (1H, d, J = 17.6 Hz), 5.36 (1H, br d, J = 3.7 Hz), 5.72 (1H, br d, J = 3.7 Hz), 6.32 (1H, dd, J = 17.6, 10.6 Hz).

Diels–Alder Reaction of 1c with MVK at 150 °C A thick-walled Pyrex tube was charged with a mixture of **1c**[6] (1 g), MVK (0.68 g) and a few crystals of hydroquinone. After degassing with an ultrasonic cleaner, the tube was filled with argon and sealed. The sealed tube was heated at 150 °C for 48 h. After being cooled, the tube was opened and ether was added. The ether extract was filtered through a pad of silica gel and concentrated under reduced pressure to leave a viscous oil. The oil (1.542 g) was separated into three fractions by chromatography on silica gel using hexane–ether. Elution with hexane–ether (10 : 1) afforded 125 mg of **6b** (9%). *Rf*: 0.31 (ether–hexane = 1 : 1). IR ν_{max}^{KBr} cm^{-1}: 1740 (sh), 1734, 1714, 1250, 1240 (sh). $C_{14}H_{20}O_3$ (M_r 236). EI-MS *m/z*: 176 ($M^+ - 60$), 133, 91. CI-MS *m/z*: 237 (MH^+), 177 ($MH^+ - 60$). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.18 (3H, s), 2.58 (1H, ddd, J = 10, 10, 4 Hz), 2.77 (1H, d, J = 10 Hz), 5.06 (1H, br s), 5.57 (1H, br s). Further elution with hexane–ether (1 : 1) gave 800 mg (56%) of an oil. TLC: homogeneous. IR ν_{max}^{KBr} cm^{-1}: 1745 (br), 1735, 1715, 1241 (br), 1026. $C_{14}H_{20}O_3$ (M_r 236). EI-MS *m/z*: 176 ($M^+ - 60$), 133 ($M^+ - 60 - 43$), 91 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s), 2.19 (3H + 1H, s), 2.09 (1H, s), 2.48 (1H + 1/3 H, m), 2.73 (1H, br t, J = 10 Hz), 4.42 (1H + 1/3H, ddd, J = 10.5, 10.5, 4 Hz), 5.60 (1H + 1/3H, br s). The ^{1}H-NMR spectrum showed that this fraction consists of a mixture of isomers of **3a** and **4a** (3 : 1). The last fraction afforded 40 mg of **6a** (5%) as an oil. IR ν_{max}^{KBr} cm^{-1}: 1738, 1708, 1237. $C_{14}H_{20}O_3$ (M_r 236). CI-MS *m/z*: 237 (MH^+). High-resolution MS *m/z*: 236.1404 (Calcd for $C_{14}H_{20}O_3$: 236.1409). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s), 2.18 (3H, s), 2.65—2.78 (3H, m), 4.88 (1H, br d, J = 2.2 Hz), 5.65 (1H, d, J = 5.5 Hz).

Hydrolysis of the Major Fraction (3a + 4a) of the Diels–Alder Products with 5% KOH–Dioxane A solution of the major fraction described above was treated with 5% KOH–dioxane (1 : 2) at room temperature overnight. The mixture was acidified with 2 M HCl under cooling in an ice-bath, extracted with ether (× 3), washed with saturated NaCl and dried ($MgSO_4$). Removal of the solvent left a crude oil (750 mg), which was purified by chromatography on silica gel using hexane–ether as an eluant. The less polar fraction gave 430 mg (52.3%) of **3d** as the major product, which was recrystallized from ether–hexane to give fine needles, mp 99—100 °C. IR ν_{max}^{KBr} cm^{-1}: 3480, 3305 (sh), 1707, 1671, 1052, 1041. High-resolution MS *m/z*: 194.1355 (Calcd for $C_{12}H_{18}O_2$: 194.1307). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, 10-CH_3), 2.48 (1H, t, J = 9 Hz, 8-H), 2.64 (1H, ddd, J = 3, 9, 11.5 Hz, 1-H), 3.14 (1H, ddd, J = 10.5, 10.5, 4 Hz, 7-H), 5.55 (1H, br s, 5-H).

The more polar fraction afforded 14 mg (17%) of **4b**. IR ν_{max}^{KBr} cm^{-1}: 3481, 3311 (sh), 1703, 1670 (w), 1057, 1051, 1046. $C_{12}H_{18}O_2$ (M_r 194). EI-MS *m/z*: 194 (M^+), 176 ($M^+ - H_2O$). A part of the sample was acetylated in the usual manner using Ac_2O–pyridine to give the corresponding acetate, which was found to be identical with the minor component (**4a**) of the major fraction by comparison of the NMR spectra.

Diels–Alder Reaction of 1c with MVK at 110 °C The reaction and work-up were done in the same manner as described above except for the reaction temperature using 1.024 g of **1c** and 1.1 g of MVK. The crude product was separated by chromatography on silica gel using hexane–ether. The less polar fraction afforded *ca.* 1.1 g of an oil (*Rf* 0.38). As this oil was still contaminated by **6a**, it was again chromatographed on silica gel to give rise to 925 mg (63.6%) of an oil (TLC homogeneous) (*Rf* 0.38) and 101 mg (*ca.* 6.9%) of **6a**. The NMR spectrum of the former showed a set of peaks at 1.94 (3H, s, 10-H), 2.24 (3H, s, OAc), and 4.74 (1H, ddd, J = 10.5, 10.5, 4 Hz, 1-H) assignable to **3b** as well as the corresponding peaks of **3a** [1.99 (3H, s, 10-H), 2.19 (3H, s, OAc) and 4.43 (1H, ddd, J = 10.5, 10.5, 4.2 Hz, 1-H)] and **4a** [2.09 (3H, s, 10-H), 2.19 (3H, s, OAc), and 4.42 (1H, ddd, J = 10.5, 10.5, 4 Hz, 1-H)]. The ratio of **3b** : **3a** : **4a** (39 : 7 : 19) was estimated by comparison of peak heights and integrations of methyl peaks and 1-H protons as mentioned above. The more polar fraction gave *ca.* 155 mg (10.6%) of **6a**.

Hydrolysis of the Diels–Alder Product (*Rf* 0.38) Obtained at 110 °C A solution of 100 mg of an oil (*Rf* 0.38) obtained by the Diels–Alder reaction mentioned above at 110 °C in dioxane (2 ml) and 5% KOH (2 ml) was stirred at room temperature overnight. After addition of dilute HCl, the mixture was extracted with ether, and the extract was washed with saturated NaCl and dried over $MgSO_4$. Evaporation of the solvent left a crystalline solid. The crude crystals were subjected to chromatography on silica gel using a hexane–ether gradient. The less polar fraction furnished *ca.* 69 mg of **3d**, whose IR spectrum was identical with that of an authentic sample. The more polar fraction gave 23 mg of **4b**. The ratio of **3d** : **4b** (69 : 23) was almost identical with that of **3a** + **3b** : **4a**.

Acetylation of 3d with Ac_2O–Pyridine A solution of **3d** (20 mg) in dry pyridine (2 drops) and Ac_2O (2 drops) was stirred at room temperature overnight under an argon atmosphere. After removal of the solvent using a vacuum pump, the residue was taken up in ether. This solution was passed through a short column of silica gel, and dried ($MgSO_4$). Evaporation of the solvent left 26 mg of an oil, which crystallized gradually when it was allowed to stand at room temperature. Recrystallization from hexane gave colorless prisms, mp 55—56 °C. IR ν_{max}^{KBr} cm^{-1}: 1731, 1710, 1669 (w), 1253. $C_{14}H_{20}O_3$ (M_r 236). EI-MS *m/z*: 176 ($M^+ - 60$), 133 ($M^+ - 60 - C_2H_3O$), 91. High-resolution MS *m/z*: 176.1189 (Calcd. for $C_{12}H_{16}O$: 176.1199). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s, 10-CH_3), 2.19 (3H, s, –OAC), 2.48 (1H, ddd, J = 11, 8, 3 Hz, 8-H), 2.72 (1H, t, J = 10 Hz, 8a-H), 4.42 (1H, ddd, J = 10.5, 10.5, 4.2 Hz, 1-H), 5.6 (1H, br s, 5-H). NMR comparison showed that this acetate corresponded to the predominant component (**3a**) of the major fraction (3 : 1 mixture).

Preparation of 3e with *p*-Bromobenzoyl Chloride and Pyridine *p*-Bromobenzoyl chloride (30 mg) was added to a solution of 20 mg of **3e** in dry pyridine (0.5 ml). The mixture was stirred at room temperature overnight under an argon atmosphere. As TLC showed that the reaction was not complete, a catalytic amount of *p*-dimethylaminopyridine was added, and the mixture was stirred for an additional 5 h. After removal of the solvent under reduced pressure, H_2O was added and the resulting mixture was extracted with ether. The ether extract was washed with H_2O and dried ($MgSO_4$). Removal of the solvent left a crystalline mass, which was dissolved in EtOAc and passed through a short column of silica gel. The eluate was concentrated and chromatographed on silica gel using hexane–ether (10 : 1) to give 21 mg of **3e**. An analytical sample was obtained by recrystallization from ether–hexane, mp 131—133 °C (prism). IR ν_{max}^{KBr} cm^{-1}: 1716, 1710, 1675, 1589, 1281, 1270, 768. $C_{19}H_{21}BrO_3$ (M_r 377). High-resolution MS *m/z*: 377.0687 (Calcd for $C_{19}H_{22}BrO_3$: 377.0748), 379.0800 (Calcd for $C_{19}H_{22}BrO_3$: 379.0730). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, s, 10-CH_3), 2.56 (1H, ddd, J = 11, 8, 3 Hz, 8-H), 2.99 (1H, t, J = 10 Hz, 8*a*-H), 4.85 (1H, ddd, J = 10.5, 10.5, 4.2 Hz, 1-H), 7.64, 7.89 (2H × 2, each d, J = 8 Hz, arom.).

The Transformation of 6a to 6b Saturated K_2CO_3 (2 drops) was added to a stirred solution of **6a** (120 mg) in MeOH (3 ml). The mixture was stirred for 4 h at room temperature. Dilute HCl was added to the mixture and the solvent was removed under reduced pressure. The residue was taken up in ether, and the solution was dried ($MgSO_4$) and evaporated to give an oil, which was chromatographed on silica gel. This procedure gave 51 mg of an oil whose IR spectrum was identical with that of **6b**.

X-Ray Crystallography of 3e The crystal data of **3e** are as follows: $C_{19}H_{21}BrO_3$ (M_r 377). Orthogonal, space group $P1$, Z = 2, D = 1.620 g cm^{-1}. Lattice constants, a = 10.159, b = 9.502, c = 9.237 Å, V = 859.5 Å^3. X-Ray diffraction measurement was carried out on a Phillips 1100 diffractometer using Cu K_α radiation monochromated by a graphite plate. Intensities of 2777 reflections were collected. The crystal structure was solved by the direct method and refined by block-diagonal-matrix least-squares calculations. The final R value was reduced to 0.032.[9]

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7) At 80 °C (benzene), the reaction was sluggish and the yield was poor (*ca.* 10%). The product ratios of **3a** : **3b** : **4a** : **6b** : **6a** at 90 °, 110 °, and 150 °C were 44 : 8 : 11 : 0 : 14, 39 : 7 : 19 : 0 : 17 and 0 : 42 : 14 : 9 : 5, respectively.
8) The article will soon be published elsewhere.
9) The final atomic parameters will be included in the Cambridge Crystallographic Data File and a list of the structure factors may be obtained upon request from one of the authors (Y.I.).