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Core Structure of Eremophilanes and Bakkanes through Niobium Catalyzed Diels−Alder Reaction: Synthesis of (±)-Bakkenolide A

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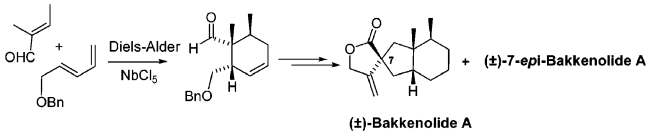

A suitable intermediate for the synthesis of eremophilanes and bakkanes was prepared by a highly regioselective and stereoselective one-step synthesis through a niobium catalyzed Diels−Alder reaction. As a demonstration of the versatility of this intermediate, a total synthesis of (±)-bakkenolide A is described.

Eremophilanes are sesquiterpene natural products derived biosynthetically by rearrangement of eudesmanes, containing a *cis*-decalin system with an uncommon *cis*-1,2-dimethyl substitution pattern.[1] Bakkane sesquiterpenes comprise a relatively rare class of natural products biosynthetically derived from the eremophilanes. The bakkanes contain a β-methylene-γ-butyrolactone spiro ring fused to a *cis*-dimethyl-*cis*-hydrindane carbon skeleton;[2] bakkenolide A (**1**) is the most well-known member (Figure 1).[3]

Several different biological activities have been described for eremophilanes and bakkanes.[2] Bakkenolide A (**1**), for instance, shows cytotoxic activity,[4] as well as influences on larval growth.[5] This natural product was isolated for the first time from the stems of a Japanese plant of the Compositae family (*Petasites japonicus*); two research groups realized the isolation independently. Kitahara et al.[3a] named the new product after the local name of the plant ("*bakke*"). Similarly, Naya et al.[3b] used another local name ("*fuki*") of the plant, proposing the nowadays less used name "fukinanolide" for this natural product.

Since the first synthesis of bakkenolide A (**1**) by Evans,[6] a number of alternative syntheses, more or less efficient, have been described.[7] The challenging structural features of these compounds have also attracted the attention of our research group; in a number of papers we have described the synthesis of model β-methylene-γ-spirolactones[8] and some efforts toward the use of the Diels−Alder reaction for building the main frame.[9]

Recently, we have become interested in investigating the use of niobium pentachloride as a Lewis acid catalyst for a number of reactions.[10] We have found that many Diels−Alder reactions are highly accelerated by $NbCl_5$ and can be carried out even at a temperature of −78 °C,[11] thus markedly improving stereoselectivity and regioselectivity, as well as reducing polymerization byproducts. We have thus sought a novel method of producing the eremophilane and bakkane skeleton using this catalyst and obtained excellent results. We have synthesized for the first time the intermediate **4,** containing all the main relative stereochemistry of eremophilanes and bakkanes and having reactive functionalities which allow its transformation into most of these natural products. As a demonstration of the versatility of compound **4**, we have carried out the synthesis of (±)-bakkenolide A (**1**) from **4** incorporating one of our previously described methods for preparing the β-methylene-γ-spirolactone moiety.[8] Diene **3** was prepared from the corresponding alcohol[12] by protection of the hydroxyl group with the benzyl group.[13] The synthesis of the adduct **4** was realized through the Diels−

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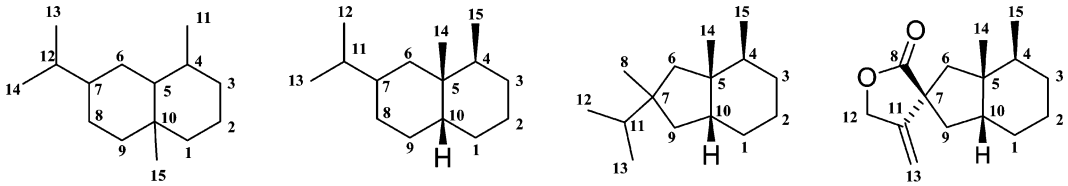
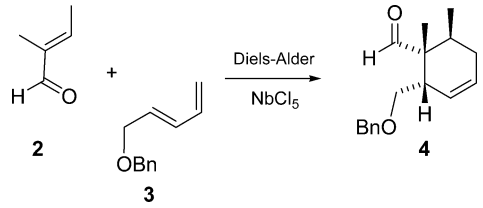
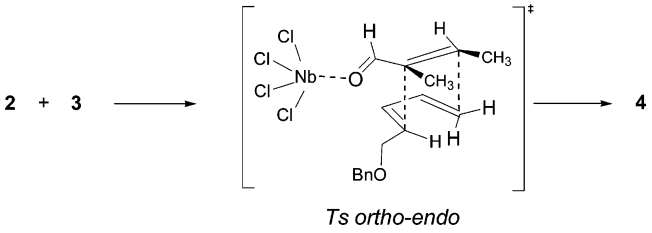


FIGURE 1. Natural products with similar core structures.

SCHEME 1. Structural Model for the Synthesis of Eremophilane and Bakkane Systems



SCHEME 2. Regioselective and Stereoselective Diels−Alder Reaction Catalyzed by $NbCl_5$



Alder reaction between diene **3** and tiglic aldehyde (**2**) in anhydrous dichloromethane, using $NbCl_5$ (0.25 equiv) as a catalyst (Scheme 1). Product **4** is formed through an ortho-endo transition state, usually favored with this type of substrate (Scheme 2).

The one-step preparation of a *cis*-1,2-dimethylated cyclohexane, already properly substituted to allow further transformations, with high regioselectivity and stereoselectivity, is the most remarkable aspect of this process. Compounds **2** and **3** do not react in the absence of Lewis acids; the role of $NbCl_5$ is very important because it increases reactivity so much that it can now be carried out from −78 to −50 °C, thus reducing diene polymerization and improving stereoselectivity (Scheme 3). Product **4** was isolated by silica gel chromatography with 45% yield. For the purpose of synthesizing bakkenolide A, however, it is more convenient to reduce the crude product directly with $LiAlH_4$, thus obtaining alcohol **5** in 42% yield over two steps, because reduction of purified **4** with $LiAlH_4$ (84% yield) gives a lower (38%) overall yield.

The reduction of the double bond of **5** and the hydrogenolysis of its benzyl ether were accomplished in one step by treatment with hydrogen and Pd−C.[15] The resulting diol **6** was transformed into the corresponding diiodide **7** with Me_3SiI,[7e] thus avoiding possible complications that usually occur when treating 1,4-diols with PX_3.[16]

From this point on, we have used essentially the same methodology previously described for the model compound,[8a,d] except that now we have additional stereochemical issues to take into account.

Alkylation of **7** with the anion of methyl 3,3-dimethylacrylate proceeded with high chemoselectivity: only the products alkylated at the less-hindered iodide were isolated (85% yield of the mixture of **8a** and **8b,** epimers at α-carbonyl carbon). This relative stereochemistry is irrelevant for the synthesis, as both epimers will give the same enolate during the ring closure step; we could therefore use the mixture directly, thus avoiding a tedious separation process which was carried out only for analytical purposes.

The cyclization process, on the other hand, produces a new stereogenic center that is a matter of major concern: only the epimer **10**, obtained as minor product, could give (±)-bakkenolide A (**1**). Examining a molecular model of the enolate from **8**, we could see that the preference for the transformation of this enolate into **10** or **11** should be determined by the difference in steric hindrance between the groups CO_2R and $C(CH_3)$═CH_2; it seems that a larger ester group would improve the preference for the desired epimer **10**.

These considerations were confirmed when we were able to improve the ratio of epimers from 18:82 (**10**/**11**) to 50:50 (**12**/**13**) just by changing the ester group from $-CO_2Me$ to $-CO_2t$-Bu.

For the following steps, we have used the mixture of epimers (**12**/**13**): treatment with NBS followed by lactonization with Ag_2O gave a mixture of (±)-bakkenolide A (**1**) and (±)-7-*epi*-bakkenolide A (**16**) in 65% yield and thus 13.3% overall yield in eight steps. As already described in the literature,[7d] (±)-bakkenolide A (**1**) can be obtained from this mixture. For analytical purposes we have realized the separation by HPLC.

In conclusion, compound **4**, a useful intermediate for the synthesis of bakkanes and eremophilanes, was prepared through a low-temperature niobium pentachloride catalyzed Diels−Alder reaction. A notable aspect of this reaction is the production, in just one step, of three stereogenic centers with the correct relative configuration and with high regioselectivity. The parent bakkane, bakkenolide A, was prepared in racemic form in 10 steps from β-vinylacrylic acid. The overall yield of a 1:1 mixture of (±)-bakkenolide A and its epimer at C7 is 8.9%.

Experimental Section

(±)-{(1*R*,2*S*,6*S*)-2-[(Benzyloxy)methyl]-1,6-dimethylcyclohex-3-en-1-yl}methanol (5) Obtained Directly from 2 and 3. To a solution of $NbCl_5$ (405 mg, 1.50 mmol) in 7 mL of CH_2Cl_2 at −78 °C was added a solution of tiglic aldehyde **2** (2.02 g, 24.0 mmol) in 7 mL of CH_2Cl_2 at −78 °C. After the mixture was stirred for 2 min, we added a solution of diene **3** (1.05 g, 6.00 mmol) in 7 mL of CH_2Cl_2 at −78 °C. After 30 min, the temperature was raised to −50 °C and the stirring was maintained for 72 h. After that, water

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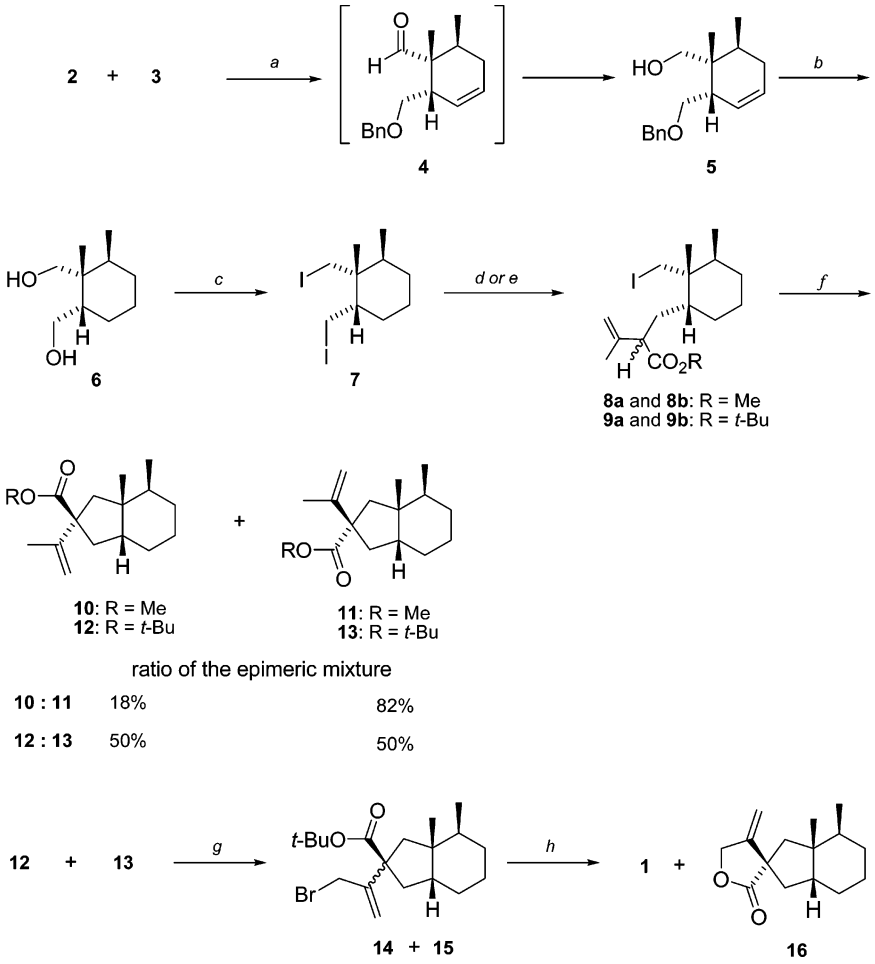
SCHEME 3. Synthesis of (±)-Bakkenolide A (1) and 7-*epi*-(±)-Bakkenolide A (16)[a]



[a] Conditions: (a) (i) $NbCl_5$, CH_2Cl_2, −78 °C → −50 °C, 72 h; (ii) $LiAlH_4$, THF, 0 °C, 1 h (42%, two steps). (b) H_2, Pd−C, ethanol, 4 atm, 4 h (99%). (c) Me_3SiI, $CHCl_3$, rt, 120 h (70%). (d) Methyl 3,3-dimethylacrylate, LDA/HMPA/THF, −78 °C → 0 °C, 30 min (85% of diastereoisomeric mixture). (e) *tert*-Butyl 3,3-dimethylacrylate,[14] LDA/HMPA/THF, −78 °C → 0 °C, 30 min (92% of diastereoisomeric mixture). (f) LDA/HMPA/THF, −78 °C (3 h for R = Me in 57% yield; 7 h for R = *t*-Bu in 77% yield). (g) NBS, benzoyl peroxide, CCl_4, hν, 3 h (95%). (h) Ag_2O, CCl_4, reflux, 3 h (68%).

(20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phase was washed with brine and dried ($MgSO_4$). After solvent evaporation, the crude product was dissolved in 20 mL of THF and added to a suspension of $LiAlH_4$ (1.0 g, 25 mmol) in 20 mL of THF at 0 °C. The reaction mixture was stirred for 1 h and quenched with water (50 mL) at 0 °C. The aqueous phase was extracted with ether (4 × 50 mL), and the combined organic layer was washed with brine and dried ($MgSO_4$). After solvent evaporation, the clear oil was purified by column chromatography (silica gel, hexanes with 5% ethyl acetate) to afford the alcohol **5** (656 mg, 2.52 mmol) in 42% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.82 (d, 3H, J = 6.6 Hz), 0.89 (s, 3H), 1.60−1.74 (m, 2H), 1.94 (dddd, 1H, J_1 = 13.0 Hz, J_2 = 4.8 Hz, J_3 = 2.3 Hz, and J_4 = 1.0 Hz), 2.27 (dddd, 1H, J_1 = 8.8 Hz, J_2 = 5.2 Hz, J_3 = 2.4 Hz, and J_4 = 1.7 Hz), 3.36 (dd, 1H, J_1 = 10.1 Hz and J_2 = 2.4 Hz), 3.38 (d, 1H, J = 11.9 Hz), 3.50 (d, 1H, J = 11.9 Hz), 3.55 (dd, 1H, J_1 = 10.1 Hz and J_2 = 8.8 Hz), 4.53 (br, 2H), 5.48 (ddt, 1H, J_1 = 10.0 Hz, J_2 = 5.2 Hz, and J_3 = 1.0 Hz), 5.65 (ddt, 1H, J_1 = 10.0 Hz, J_2 = 4.8 Hz, and J_3 = 1.7 Hz), 7.27−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 15.0 (CH_3), 16.1 (CH_3), 29.3 (CH), 31.9 (CH_2), 39.0 (C), 43.7 (CH), 68.2 (CH_2), 71.0 (CH_2), 73.6 (CH_2), 126.4 (CH), 128.0 (CH), 128.0 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 137.2 (C). IR ν_{max} (neat KBr) (cm^{-1}): 698, 736, 1092, 1494, 2880, 2962, 3024, 3140−3658. HRMS (ESI−TOF): calculated for $C_{17}H_{25}O_2^+$ (MH^+), 261.1849; found, 261.1859 (Δ = 3.8 ppm). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.80; H, 9.54.

(±)-(2*S*) and (±)-(2*R*)-*tert*-Butyl 2-{[(1*R*,2*R*,3*S*)-2-(Iodomethyl)-2,3-dimethyl-cyclohexyl]methyl}-3-methylbut-3-enoate (9a) and (9b). To a solution of diisopropylamine (0.33 mL, 239 mg, 2.36 mmol) in 4 mL of THF at 0 °C was added 1.00 mL (2.15 mmol) of a 2.15 mol/L solution of *n*-butyllithium in hexanes. The mixture was stirred for 15 min, and HMPA (0.46 mL, 2.65 mmol) was added and stirred for an additional time of 15 min. The solution of LDA/HMPA was cooled to −78 °C, and a solution of *tert*-butyl 3,3-dimethylacrylate (343 mg, 2.20 mmol) in 0.5 mL of THF was added and stirred for 20 min. The diiodide **7** (420 mg, 1.07 mmol) in 2 mL of THF cooled to −78 °C was then added, and the reaction mixture was stirred for 3 min. The temperature of the reaction system was slowly increased up to 0 °C (∼30 min), and the mixture was stirred for 30 min. The reaction was quenched with water (20 mL), and the aqueous phase was extracted with ether (3 × 40 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). After solvent evaporation, the yellow oil was purified by column chromatography (silica gel, hexanes with 5% ethyl acetate) to afford a mixture of diastereoisomers **9a** and **9b** (416 mg, 0.99 mmol) in 92% yield. The analysis of **9a**/**9b** was realized by comparison of the ^{1}H NMR data of the mixture of **8a**/**8b**. IR ν_{max} (neat KBr) (cm^{-1}): 896, 1148, 1460, 1648, 1726, 2930, 2972.

HRMS (ESI−TOF): calculated for $C_{19}H_{34}IO_2^+$ (MH^+), 421.1598; found, 421.1585 (Δ = 3.1 ppm).

(±)-*tert*-Butyl (2*R*,3a*R*,4*S*,7a*R*)-2-Isopropenyl-3a,4-dimethyl-octahydro-1*H*-indene-2-carboxylate (12) and (±)-*tert*-Butyl(2*S*,3a*R*,4*S*,7a*R*)-2-Isopropenyl-3a,4-dimethyloctahydro-1*H*-indene-2-carboxylate (13). To a solution of diisopropylamine (0.35 mL, 253 mg, 2.50 mmol) in 4 mL of THF at 0 °C was added 1.10 mL (2.32 mmol, 2.10 mol/L) of a solution of *n*-butyllithium in hexanes. The mixture was stirred at 15 min, and HMPA (0.42 mL, 2.40 mmol) was added and stirred for 15 min. The solution of LDA/HMPA was cooled to −78 °C, a solution of **9a/9b** (490 mg, 1.16 mmol) in 2.5 mL of THF cooled to −78 °C was added, and the reaction mixture was then stirred for 7 h. The temperature of the reaction system was slowly increased up to 0 °C (∼30 min) and then quenched with water (20 mL). The aqueous phase was extracted with ether (3 × 40 mL), and the combined organic phases were washed with brine and dried ($MgSO_4$). After solvent evaporation, the yellow oil was purified by column chromatography (silica gel, hexanes with 5% ethyl acetate) to afford a mixture of **12** and **13** in a ratio of 1:1 (270 mg, 0.89 mmol) in 77% yield. This proportion was determined by analysis of the ^{1}H NMR data of the epimeric mixture. IR ν_{max} (neat KBr) (cm^{-1}): 1152, 1460, 1638, 1720, 2926, 2964. HRMS (ESI−TOF): calculated for $C_{19}H_{33}O_2^+$ (MH^+), 293.2475; found, 293.2471 (Δ = 1.4 ppm).

(±)-Bakkenolide A (1) and (±)-7-*epi*-Bakkenolide (A) (16). To a solution of esters **14** and **15** (70 mg, 0.19 mmol, 1:1 epimeric mixture) in 3 mL of CCl_4 was added 130 mg (0.56 mmol) of Ag_2O. The reaction mixture was refluxed for 3.5 h. The solid residue was filtered (silica gel and celite layer) and washed with CCl_4 (3 × 5 mL). After solvent evaporation, the yellow oil was purified by column chromatography (silica gel, hexanes with 5% ethyl acetate) to afford a mixture of epimers **1** and **16** in a 1:1 ratio. The natural product **1** and the epi-isomer **16** were separated by HPLC (UV−vis at 212 nm detector) with an analytical column (4.6 cm internal diameter and 25 cm length with 5 mm particles and 100 Å of pore) using hexane as an eluent (0.5 mL min^{-1}). (±)−*Bakkenolide A* (**1**).[7d−f] ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.85 (d, 3H, J = 6.8 Hz), 0.99 (s, 3H), 1.10−1.22 (m, 1H), 1.40−1.68 (m, 6H), 1.95 (d, 1H, J = 14.2 Hz), 1.98 (dd, 1H, J_1 = 12.9 Hz and J_2 = 7.0 Hz), 1.98 (d, 1H, J = 14.2 Hz), 2.09 (dd, 1H, J_1 = 13.3 Hz and J_2 = 12.9 Hz), 2.27 (dddd, 1H, J_1 = 13.3 Hz, J_2 = 7.0 Hz, J_3 = 4.9 Hz, and J_4 = 2.3 Hz), 4.74 (ddd, 1H, J_1 = 12.8 Hz, J_2 = 2.3 Hz, and J_3 = 2.1 Hz), 4.80 (ddd, 1H, J_1 = 12.8 Hz, J_2 = 2.3 Hz, and J_3 = 2.1 Hz), 5.03 (t, 1H, J = 2.1 Hz), 5.11 (t, 1H, J = 2.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.4 (CH_3), 19.2 (CH_3), 21.0 (CH_2), 23.3 (CH_3), 30.9 (CH_2), 33.9 (CH), 42.4 (CH_2), 44.0 (C), 46.2 (CH), 48.5 (CH_2), 49.9 (C), 70.4 (CH_2), 105.8 (CH_2), 150.4 (C), 182.6 (C). (±)**7**−*epi-Bakkenolide A* (**16**).[7d] ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.82 (d, 3H, J = 6.7 Hz), 0.97 (s, 3H), 1.02−1.18 (m, 1H), 1.42−1.65 (m, 5H), 1.52 (d, 1H, J = 14.1 Hz), 1.66 (dd, 1H, J_1 = 12.5 Hz and J_2 = 6.6 Hz), 1.91 (dqd, 1H, J_1 = 12.5 Hz, J_2 = 6.7 Hz, and J_3 = 3.0 Hz), 1.95−2.03 (m, 1H), 2.40 (d, 1H, J = 14.1 Hz), 2.46 (dd, 1H, J_1 = 13.7 Hz and J_2 = 12.5 Hz), 4.76 (ddd, 1H, J_1 = 12.9 Hz, J_2 = 2.2 Hz, and J_3 = 1.8 Hz), 4.81 (dd, 1H, J_1 = 12.9 Hz, J_2 = 2.2 Hz, and J_3 = 1.8 Hz), 4.99 (t, 1H, J = 1.8 Hz), 5.07 (t, 1H, J = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.6 (CH_3), 19.7 (CH_3), 21.0 (CH_2), 23.6 (CH_3), 30.8 (CH_2), 33.0 (CH), 41.5 (CH_2), 44.1 (C), 46.9 (CH), 50.0 (C), 50.1 (CH_2), 70.1 (CH_2), 105.5 (CH_2), 152.0 (C), 182.3 (C). IR ν_{max} (neat KBr) (cm^{-1}): 894, 1030, 1124, 1236, 1462, 1672, 1778, 2958. HRMS (ESI−TOF): calculated for $C_{15}H_{23}O_2^+$ (MH^+), 235.1693; found, 235.1695 (Δ = 0.8 ppm).

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Supporting Information Available: The detailed experimental section includes the transformations of **2** + **3** to **4, 5** to **6, 6** to **7, 7** to **8a/8b, 8a/8b** to **10/11,** and **12/13** to **14/15** and ^{1}H NMR and ^{13}C NMR spectra for key intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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