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[12] Ga-Na-bis(binaphthoxide)[20] (41 % yield, 52 % *ee*), alkali metal-free Ga-bis(binaphthoxide)[21] (22 % yield, 37 % *ee*), or Al-Li-bis(binaphthoxide)[22] (20 % yield, 72 % *ee*) gave much less satisfactory results.

[13] The use of 10,10′-dihydroxy-9,9′-biphenanthryl,[23] 3,3′-dihydroxy-4,4′-biphenanthryl (BIPOL),[24] and α,α,α′,α′-tetraphenyl-2-methyl-2-phenyl-1,3-dioxolane-4,5-dimethanol (TADDOL)[25] gave unsatisfactory results.

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[16] GaSO was prepared in a similar manner to GaLB (from a 1:2 ratio of $GaCl_3$ and disodium H_8-binaphthoxide). This ratio was found to give the maximum reactivity and enantiomeric excess. The influence of the ratio of $GaCl_3$ and disodium H_8-binaphthoxide on the reaction of **3** with **1** at 50 °C is as follows: 1:1 (10 % yield, 30 % *ee*), 1:1.5 (53 % yield, 53 % *ee*), 1:2 (73 % yield, 56 % *ee*), 1:2.5 (65 % yield, 49 % *ee*), 1:3 (trace). The structure of GaSO is supported by positive-ion laser-desorption/ionization time-of-flight mass spectrometry (LDI-TOF; reflectron mode): *m*/*z*: 701 ([M^++Na] for ^{71}Ga).

[17] Ga-Li-bis(H_8-binaphthoxide) (39 % yield, 33 % *ee*) and Ga-K-bis(H_8-binaphthoxide) (58 % yield, 52 % *ee*) gave less satisfactory results.

[18] By comparison with Takaya's catalytic enantioselective hydrogenations with the H_8-(*S*)-[2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl] complex (H_8-BINAP), T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya, *J. Org. Chem.* **1996**, *61*, 5510 – 5516.

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[21] This complex was prepared from $GaCl_3$ (1 mmol), 1,1′-(*R*)-binaphthol (2 mmol), and *n*BuLi (3 mmol) in THF at room temperature.

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Total Synthesis of Chatancin**

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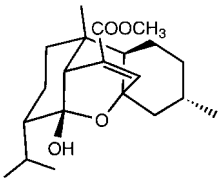
Chatancin (**1**) was discovered within a large program to screen physiologically active compounds from marine invertebrates.[1] This tetracyclic diterpene, which is isolated from a soft coral (*Sarcophyton sp.*), is an antagonist of the platelet activating factor (PAF) and thus of potential use against hypotension and respiratory, inflammatory, and cardiovascular diseases.[2] The physiological activity as well as the fact that this oxygen-bridged dodecahydrophenanthrene derivative with its unusual substitution pattern and the seven stereogenic centers has never been synthesized so far prompted us to look for a suitable stereoselective access to **1**.



chatancin **1**

We chose a protocol for the stereoselective preparation of substituted *cis*-decalinones developed in our laboratory[3] to achieve the highly stereoselective generation of four of the seven stereogenic centers of **1** starting from easily available symmetrical compounds. To develop an enantiomerically pure synthesis the third carbocycle was fashioned by attaching a small chiral side chain that is readily accessible from methyl (R)-3-hydroxyisobutyrate.[4] Thus five of the seven stereogenic centers of **1** could be established. This part of our synthetic efforts has been published earlier.[5] Starting with thymoquinone and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene the tricyclic Diels – Alder adduct was formed, which was converted into the tetracyclic ketone (±)-**2** by stereo- and regioselective group transformations. Racemic (±)-**2** was allowed to react with (*S*)-3-lithio-2-methyl-1-benzyloxypropane to yield the diastereomeric tertiary alcohols (+)-**3** and (−)-**4** (Scheme 1). However, attempts to save chiral reagent by using only half an equivalent of the alkyllithium compound failed. This is due to a significantly higher reaction rate for the formation of the undesired diastereomer (−)-**4** than for (+)-**3**. The structure of (−)-**4** was established unambiguously by X-ray crystal structure analysis. Twofold ring opening of the diastereomeric pair (+)-**3** and (−)-**4** under acidic conditions led to the diastereomeric *cis*-decalinones (+)-**6** and (−)-**5**, respectively. Owing to the large

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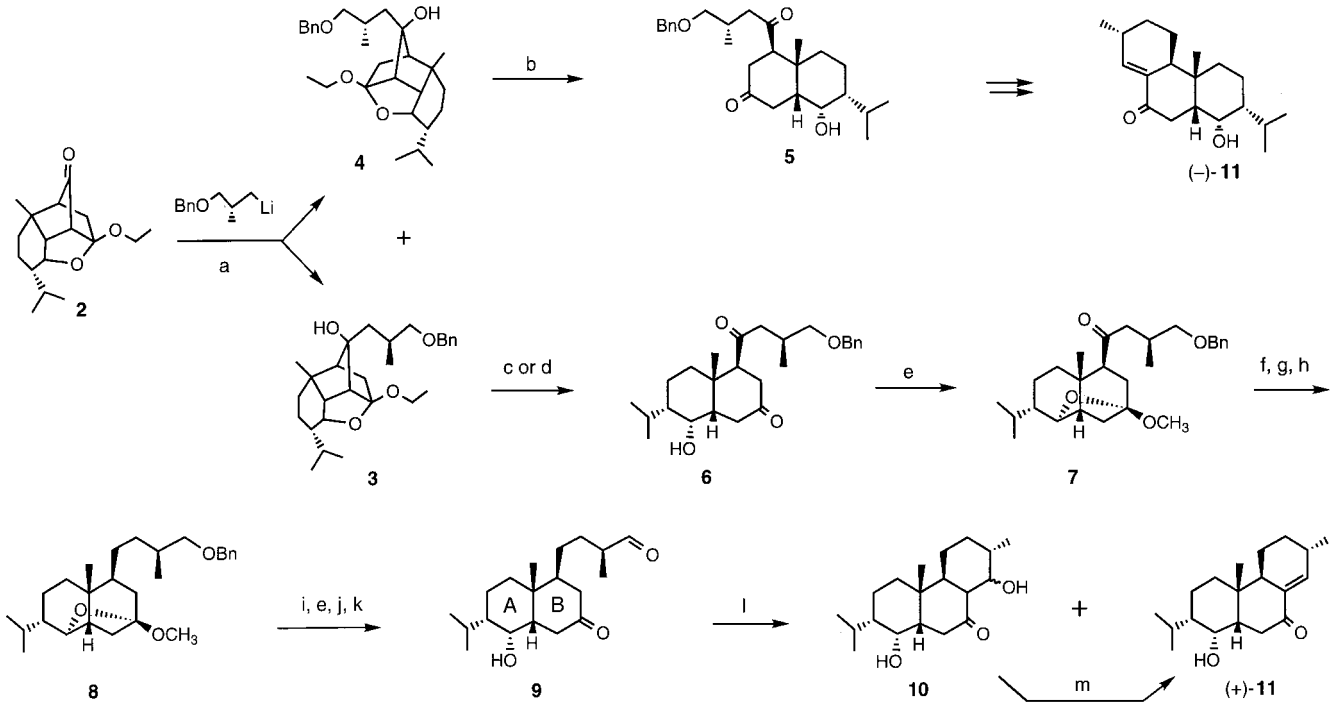

Scheme 1. a) Toluene/$O(C_2H_5)_2$ (1/2), $-60\,^{\circ}C \rightarrow$RT (room temperature); RT, 22 h, 89%; b) $BF_3 \cdot O(C_2H_5)_2$ (10 equiv), CH_3CN, $-15\,^{\circ}C$, 4 h, 85%; c) $BF_3 \cdot O(C_2H_5)_2$ (10 equiv), CH_3CN, $-15\,^{\circ}C$, 2 d, 95%; d) 5 M $LiClO_4$, H^+, $O(C_2H_5)_2$, RT, 6 h, 99%; e) $HC(OCH_3)_3$, H^+, CH_3OH, RT, 4 h, 97%; f) $LiAlH_4$, $O(C_2H_5)_2$, $0\,^{\circ}C \rightarrow$RT; RT, 4 h, 92%; g) $ClCOCOOCH_3$, C_5H_5N, DMAP, $30\,^{\circ}C$, 3 h, 97%; h) Bu_3SnH, AIBN, toluene, reflux, 8 h, 70–75%; i) H_2, Pd(10%)/C, CH_2Cl_2, RT, 15 h, 85%; j) Dess–Martin periodinane, CH_2Cl_2, RT, 2 h, 93%; k) 2% aq HCl/THF (1/1), RT, 40 min, 99%; l) KO*t*Bu, HO*t*Bu, argon, RT, 45 min; m) H^+, $CHCl_3$, argon, RT, 60 h, 86% over two steps. Bn = benzyl, DMAP = 4-dimethylaminopyridine, AIBN = azobisisobutyronitrile.

difference in the rates of fragmentation, the two decalinones could be separated kinetically.[5]

Enantiomerically pure (+)-**6**[5] is then used to synthesize the dodecahydrophenanthrenone. To achieve the deoxygenation of the now superfluous keto group of the side chain, the cyclic ketone has to be protected as the tricyclic ketal (−)-**7**. To overcome the severe steric hindrance the following strategy is chosen: Ketone (−)-**7** is reduced with lithium aluminum hydride to the epimeric alcohols, which are esterified to the mixed oxalic esters[6] and subsequently treated with tributylstannane to yield (−)-**8**.[7] Hydrogenolysis of the benzyl group is accompanied by partial ring cleavage to the hydroxy ketone. Since protection of the hydroxyl group of ring A is essential, the cyclic ketal is regenerated by treatment with methyl orthoformate in acidic methanol. Subsequently, the primary alcohol is oxidized to the aldehyde with Dess–Martin periodinane,[8] and the cyclic ketal is hydrolyzed with aqueous acid. Treatment of ketoaldehyde **9** with base leads to the oxygen-sensitive mixture of aldol (−)-**10** and enone (+)-**11**, which is completely dehydrated to (+)-**11** with acidic chloroform.

The same reaction sequence starting with the diastereomeric decalinone derivative (−)-**5** leads exclusively to enone (−)-**11** by total epimerization of the stereogenic center adjacent to the aldehyde moiety under the conditions of the aldol reaction. This unexpected result is advantageous for several reasons. First, it constitutes a stereodivergent synthesis of (+)- and (−)-**11** and, consequently, (+)-chatancin and unnatural (−)-chatancin in enantiopure form for further physiological testing without loss of starting material. Second, if only one of the two enantiomers is required, chatancin can be prepared more economically due to the fact that the alcohol **4** that is preferentially formed can be used in both cases. As a consequence, to obtain natural (+)-chatancin only half an equivalent of (*R*)-3-lithio-2-methyl-1-benzyloxypropane has to be utilized to produce enone (+)-**11** via (+)-**4**. Third, the entire starting material can be transformed into (±)-chatancin by utilizing the racemic alkyllithium compound.

Because of the preliminary difficulties we experienced with the next steps of our synthetic plan,[9] we decided to investigate the further route towards chatancin with the racemic enone (±)-**11**. Thus, 2-methyl-1,3-propanediol is converted into 3-benzyloxy-2-methylpropanol.[10] Transformation of the primary alcohol into the iodide and subsequent halogene–metal exchange with *tert*-butyllithium yields racemic 3-lithio-2-methyl-1-benzyloxypropane,[5] which is treated with ketone (±)-**2**. The diastereomeric mixture of the tertiary alcohols (±)-**3** and (±)-**4** obtained is converted into (±)-**11** as described for (+)-**11** (Scheme 2).

Enone (±)-**11** is treated with *m*-chloroperbenzoic acid to yield the *endo*-epoxide **12** through the directing effect of the *endo* hydroxyl group[11] of ring A. Thus, the sixth stereogenic center of chatancin is established. To obtain reproducible good yields it is essential to add radical scavengers, as reported by Kishi et al.[12] The keto functionality of **12** is stereoselectively reduced with sodium borohydride. To suppress the directing effect of the newly generated hydroxyl

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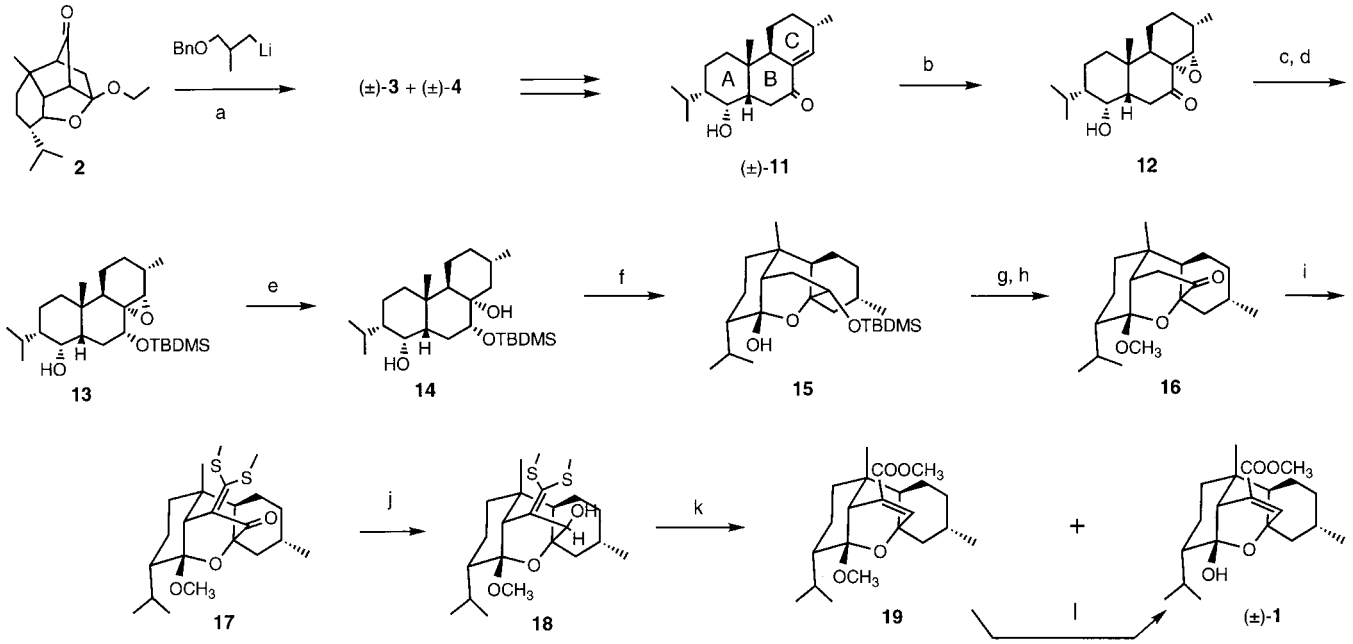

Scheme 2. a) Toluene/$O(C_2H_5)_2$ (1/2), $-60\,^{\circ}C \rightarrow$RT; RT, 22 h, 89 %; b) *m*-chloroperbenzoic acid, 2,6-di-*tert*-butyl-4-methylphenol, CH_2Cl_2, 4 °C, 12 h, 85 %; c) $NaBH_4$, CH_3OH, 0 °C $\rightarrow$RT; RT, 4 h; d) TBDMSCl, $(C_2H_5)_3N$, DMF, RT, 2 h, 70 % over two steps; e) $LiB(C_2H_5)_3H$ (8 equiv), $(C_2H_5)_2O$, reflux, 12 h, 93 %; f) Jones reagent, acetone, 0 °C, 20 min, 91 %; g) $HC(OCH_3)_3$, H^+; CH_3OH, 0 °C, 40 min, 96 %; h) Dess–Martin periodinane, CH_2Cl_2, RT, 2 h, 90 %; i) LiHMDS, HMPTA, THF, $-78\,^{\circ}C$, 1 h; CS_2, 0 °C, 2 h; LiHMDS, $-78\,^{\circ}C$, 30 min; CH_3I, RT, 2 h, 77 %; j) $LiB(C_2H_5)_3H$, $(C_2H_5)_2O$, reflux, 1 h, 99 %; k) PIFA, CH_3OH, RT, 12 h; l) 0.2 % aq HCl/THF (1/1), RT, 12 h, 30 % over two steps. TBDMS = *tert*-butyldimethylsilyl, LiHMDS = lithium bis(trimethylsilyl)amide, HMPTA = hexamethyl phosphoramide phenyliodine(III) bis(trifluoroacetate).

group in ring B, this alcohol is regioselectively protected as silylether **13** prior to the reductive epoxide cleavage. However, many attempts at selective epoxide opening were necessary. Finally, prolonged heating of **13** with a large excess of lithium triethylborohydride affords high yields of the tertiary alcohol **14**. Jones oxidation of the secondary hydroxyl group in ring A leads via the hydroxy ketone to the hemiketal **15** by spontaneous cyclization. Treatment of **15** with methyl orthoformate in acidic methanol yields the mixed cyclic ketal with simultaneous loss of the silyl group. With this ketal formation the last of the seven stereogenic centers of chatancin is established.

The secondary alcohol is then oxidized to ketone **16** to permit the introduction of the carboxylic group. All efforts to use activated carbonic acid derivatives to attach the ester group of **1** by Claisen condensation failed. Due to the severe steric hindrance only enol esters are formed. The ester group is successfully introduced with the following reaction sequence: The lithium enolate of **16** is allowed to react with carbon disulfide and is subsequently treated with methyl iodide under basic conditions. The keto group of the dimethyldithioketalketene **17** thus obtained is quantitatively reduced to the *exo*-hydroxyl group in **18**. The conversion of the dithioketalketene into the methyl carboxylate is achieved by reaction with phenyliodine(III) bis(trifluoroacetate)[13] accompanied by spontaneous dehydration to yield *O*-methylchatancin (**19**) as the main product and small amounts of chatancin ((±)-**1**). Treatment with highly diluted aqueous HCl also converts **19** into racemic chatancin. Thus, chatancin is prepared in 33 steps with an overall yield of 0.7 % starting from thymoquinone and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene. The spectroscopic data of synthetic chatancin are in full agreement with those of natural chatancin.

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