Stereospecific Total Synthesis of (±)-Cafestol

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Cafestol (1), a long known member of the ent-kaurene family, is of special interest for its biological (e.g., anti-inflammatory) activity and the widespread human consumption as a constituent of coffee. Although the structure of cafestol was clarified almost



30 years ago,¹ there has been no reported synthesis of cafestol or its more highly functionalized congeners, such as 1,2-dehydro 1 (kahweol)² and 2-keto-11 β -hydroxy 1 (mascarol).³ The first synthesis of 1 is recorded herein. The approach utilizes a novel and convergent construction of the ring system and a versatile pentacyclic intermediate which is suitably functionalized to serve as general precursor for the whole cafestol family.

1

The bicyclic ketone 2, prepared from cyclohexane-1,3-dione and chloroacetaldehyde,⁴ was methylated^{5,6} (1.1 equiv of LDA in THF at -78 °C followed by 1.1 equiv of methyl iodide at -50 °C to 0 °C for 40 min, and 0-5 °C for 20 min) to form 3 (70%)



which was then transformed into acetylene 4 (83% overall yield) by the following sequence: (1) reaction with lithiotrimethylsilylacetylene (1 h at -35 °C and 10 min at 0 °C), (2) dehydration using 1.2 equiv of pyridinium p-toluenesulfonate and excess $MgSO_4$ at reflux in benzene for 20 min, and (3) desilylation with potassium fluoride dihydrate in dimethyl sulfoxide at 15 °C for 20 min. Reaction of acetylene 4 with 1.3 equiv of disiamylborane in THF at 0 °C for 5 h and oxidation with a vigorously stirred mixture of potassium carbonate and 3% hydrogen peroxide in water at 20 °C for 5 min produced after extractive isolation aldehyde 5 which was directly reduced to the corresponding alcohol (63% from 4) with use of sodium borohydride in methanol at 0 °C for 5 min. This alcohol was converted to the corresponding iodide 6 (84%) by reaction with 1.2 equiv each of triphenyl-

(6) All reactions involving air-sensitive materials were conducted under an inert atmosphere (N_2 or Ar).

phosphine and imidazole and 1 equiv of iodine at 23 °C for 12-15 min.

Methyl cyclohexa-1,3-diene-5-carboxylate⁸ was deprotonated (1.05 equiv of LDA in THF at -60 °C for 30 min) and alkylated with iodide 6 (initially at -60 °C in THF solution with slow warming to 0 °C over 14 h) to form tricyclic ester 7 (67%).



7 $R = COOCH_3$ $R = COCH_2COOtBu$ $R = COCN_2COOtBu$ 8

Appendage extension of 7 to generate the β -keto ester 8 was accomplished in 83% overall yield by the sequence: (1) saponification of 7 (3% sodium hydroxide in 1:6:12 THF-watermethanol at 23 °C for 16 h), (2) conversion to the imidazolide (1.2 equiv of 1,1'-carbonylimidazole in THF at 23 °C for 18 h), and (3) reaction with 3 equiv of α -lithio tert-butyl acetate in THF at -78 °C for 1 h. Treatment of β -keto ester 8 with p-toluenesulfonyl azide and 1,8-diazabicyclo[5.4.0]undec-7-ene in methylene chloride at 23 °C for 1.2 h produced the corresponding diazoketone 9 (98%) which upon slow addition to a solution of copper(II) bissalicylaldehyde-tert-butylimine in toluene at reflux gave with >10:1 selectivity the somewhat labile cyclopropyl keto ester 10





in 45-50% yield.9 Reduction of 10 without purification using sodium borohydride in methanol at 0 °C for 30 min afforded after chromatography on silica gel pure hydroxy ester 11 (45% from 9, >95% from 10).¹⁰ Reaction of alcohol 11 with sodium hydride and benzyl bromide in dimethylformamide (initially at 0 °C then at 23 °C for 2 h) produced the corresponding benzyl ether (92%) which upon exposure to diisobutylaluminum hydride in methylene chloride at -10 °C for 40 min gave alcohol 12 (94%).



11 Y = OH, $X \neq COOtBu$ 12 Y = OBz, $X = CH_2OH$

A key step in the synthesis, cyclization of 12 to pentacycle 13, mp 93 °C, was accomplished stereospecifically and in 68% yield by reaction with an excess of triflic anhydride and 2,6-lutidine in methylene chloride at -78 °C for 15 min. The structure and

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(2) Kaufman, H. P.; Sen Gupta, A. K. Chem. Ber. 1963, 96, 2489.

^{(4) (}a) Matsumoto, M.; Watanabe, N. European Patent Application EP 101 003, 1984; Chem. Abstr. 1984, 101, 23319d. (b) Tochtermann, W.; Köhn, H. Chem. Ber. 1980, 113, 3249.

⁽⁵⁾ Abbreviations used herein: LDA, lithium diisopropylamide; THF tetrahydrofuran.

⁽⁷⁾ Iodide 6 is a labile substance which can be stabilized by addition of ca. 10% of triphenylphosphine. Although 6 so stabilized can be stored at -40

[°]C, it was normally used for the next step as soon as possible. (8) Hoare, J. H.; Policastro, P. O.; Berchtold, G. A. J. Am. Chem. Soc. 1983, 105, 6264.

⁽⁹⁾ Corey, E. J.; Myers, A. G. Tetrahedron Lett. 1984, 25, 3559.

⁽¹⁰⁾ A very small amount of the epimeric alcohol, which is more polar than 11 (R_j values 0.18 and 0.29, respectively, by silica gel TLC using 2:1 hexane ether), could be detected chromatographically. Analysis of the ¹H NMR spectra of 11 and epimeric alcohol allowed assignment of configuration since the carbinol proton of 11 showed a positive NOE effect with the methylene attached to the three-membered ring, an effect not observed with the epimer.

stereochemistry of 13 were confirmed unambiguously by 500-MHz



¹H NMR studies including spin decoupling and NOE measurements and also follow from the conversion to cafestol (1).¹¹ The pentacycle 13 is quite sensitive to acids and is even unstable in chloroform solution, apparently because of the vinyl furan subunit. Debenzylation of 13 was carried out by reaction with 15 equiv of lithium in 2:1 liquid ammonia-THF containing 7 equiv of ethanol at -78 °C for 30 min to give unsaturated alcohol 14 (100%). Alcohol 14 was further reduced with 5 equiv of sodium in 2:1 liquid ammonia-THF containing 5 equiv of sodium in 2:1 liquid ammonia-THF containing 5 equiv of sodium in 2:1 liquid ammonia-THF containing 5 equiv of sodium in 2:1 liquid ammonia-THF containing 5 equiv of water at -78 °C for 10 min to provide trans fused products 15 (90% yield, ratio of trans to cis product >95:5).¹²





The 11,12-double bond of **15**, though useful for the synthesis of 11-functionalized kaurenes, had to be reduced for the synthesis of cafestol itself. This operation as well as adjustment of functionality on the 16,17-bridge was conducted as follows. Alcohol **15** was converted to the allylic primary iodide **16** by mesylation



(excess mesyl chloride and triethylamine in THF at -50 °C for 40 min) and subsequent reaction with powdered zinc iodide in methylene chloride at 23 °C for 2 h (72% overall yield). Treatment of iodide 16 with excess hydrazine (97%) in 1:1 dimethoxyethane-tert-butyl alcohol for 30 min at 23 °C provided the corresponding hydrazine (17, 100%) which after isolation but without purification was stirred in methylene chloride solution with oxygen for 7 h to give diene 18 (70% overall from 16). This useful procedure for overall deoxygenation of 15 to form 18 was developed on the expectation that the allylic hydrazine 17 should be converted to 18 by oxidation, $RNHNH_2 \rightarrow RN=NH$, followed by 1,5-sigmatropic rearrangement of hydrogen with loss of nitrogen. At this stage the furan ring was protected (against hydrogenation)¹³ by lithiation (tert-butyllithium in THF at -40 °C for 30 min) and reaction with triisopropylsilyl triflate to give 19 (90% yield). Conversion 19 to 1 in 55% overall yield was accomplished by the sequence: (1) selective hydroxylation of the





exocyclic double bond using osmium tetroxide in THF at 23 °C for 5 h, (2) hydrogenation of the 11,12-double bond with hydrogen 65 psi) and 5% Rh-Al₂O₃ catalyst in THF at 23 °C for 30 h, and (3) desilylation (stirring with 5:5:1 THF-acetonitrile-48% hydrofluoric acid at 23 °C for 3.5 h). The synthetic (\pm)-1 so obtained was identical with an authentic sample of naturally derived cafestol¹⁴ with regard to silica TLC chromatographic mobility with use of several solvent systems, 500-MHz ¹H NMR, infrared, and mass spectra.

Several aspects of the synthesis of (\pm) -cafestol as described above are worthy of note. First, synthesis of chiral 7 either by enantioselective alkylation or resolution of the corresponding racemic acid, which should be realizable, would provide a route to the natural form of cafestol. The cyclization of 12 to 13, which leads to the kaurene system directly and stereospecifically, demonstrates a new and versatile approach for the synthesis of this large class of diterpenes. Finally, the stereospecific reduction of 14 to either trans or cis fused products, the conversion of 15 to 18, and the use of triisopropylsilyl as a protecting group in hydrogenation each illustrate useful new methodology.¹⁵

Supplementary Material Available: Listing of experimental data for compounds 1–19 (3 pages). Ordering information is given on any current masthead page.

Two-Directional Chain Synthesis: The Enantioselective Preparation of Syn-Skipped Polyol Chains from Meso Precursors

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There are several attractive features of the chain synthesis strategy that involves the simultaneous homologation of a nascent chain in two directions.¹ This method offers the opportunity to reduce the total number of transformations required to complete a synthesis relative to the one-directional alternative. A problem intrinsic to this strategy is that, in most cases, the termini of the chain will require differentiation. If the homologated chain is meso, terminus differentiation will necessitate an enantiotopic group selective reaction.

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⁽¹¹⁾ The cyclization to form the kaurene system is a difficult one for steric reasons, success depending crucially on substrate structure. This facet of our research will be dealt with in a separate publication.

⁽¹²⁾ Water is critical to the stereochemical outcome of this interesting reduction. Reduction of 14 with lithium in anhydrous liquid ammonia-THF at -78 °C affords stereoselectively the cis fused stereoisomer of 15 (72% isolated yield). It is possible that the stereoisomers are formed from different intermediates.

⁽¹³⁾ See: Corey E. J.; Rücker, C. Tetrahedron Lett. 1982, 23, 719.

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⁽¹⁾ For a discussion of the two-directional chain synthesis strategy, see: Schreiber, S. L. Chem. Scr., in press.