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From natural camphor to (1*R*,2*S*)-2-chloromethyl-3-oxocyclopentanecarboxylic acid: a stereocontrolled approach to enantiopure sarkomycin

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Abstract—The preparation of enantiopure (1*R*,2*S*)-2-chloromethyl-3-oxocyclopentanecarboxylic acid **9**, an interesting possible precursor of the antitumor agent sarkomycin, from a camphor-derived 3-hydroxymethylnorbornan-2-one is reported. The described procedure constitutes the first stereocontrolled approach to sarkomycin starting from commercially available natural camphor. The procedure takes place in only six steps with a high overall yield (59%). The key-step of the described procedure is the stereocontrolled ring opening of a conveniently functionalized 3-oxonorborn-1-yl triflate under a straightforward basic hydrolysis. The described route constitutes a model procedure for the preparation of other enantiopure C2-substituted 3-oxocyclopentanecarboxylic acids; which are related with the sarkomycin family of antitumor agents.

The natural product sarkomycin **1**, a cyclopentanoid antibiotic isolated from the soil microorganism *Streptomyces erythrochromogenes*,[1] is the parent member of an important class of antitumor agents such as methylenomycin A **2**, xanthocidin **3**, pentenomycin **4** and homosarkomycin **5** (Fig. 1).[2] The strong inhibitory effect of sarkomycin **1** on several human tumors such as Yoshida sarcoma, Sarcoma-180 and Hela carcinoma has resulted in its pharmacological use as antitumor agent in Russia, Japan and USA.[3] This important biological activity has made sarkomycin a relevant synthetic target. Nevertheless, although the structure of sarkomycin is very simple, a cyclopentanecarboxylic acid with only one stereogenic center (see **1** in Fig. 1), its total synthesis presents great difficulties. This is due to the fact that sarkomycin **1** itself, as well as a large number of its derivatives (e.g. sarkomycin esters), present a high chemical instability, being very sensitive to both bases and acids, undergoing dimerization and polymerization easily. This makes them not very stable, inclusively toward cold storage.[4]

Among the large number of reported sarkomycin syntheses, most are directed to the racemic mixture.[5] Moreover, due to the special instability of **1**, many of these syntheses, so-called formal syntheses, finalize at the stage of more stable sarkomycin precursors such as cyclosarkomycin **6** (Fig. 1),[6] or different sarkomycin esters.[7]

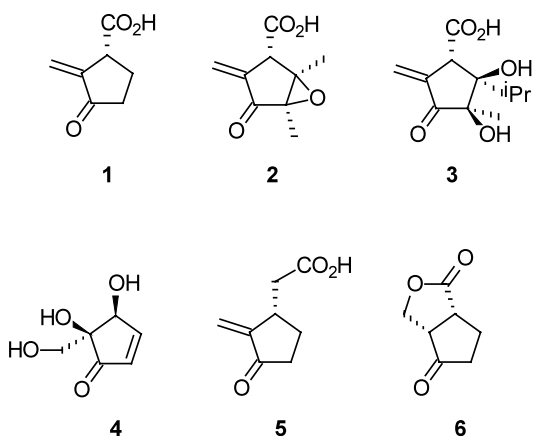

Figure 1. Some antitumor agents (**1**–**5**) of the sarkomycin family.

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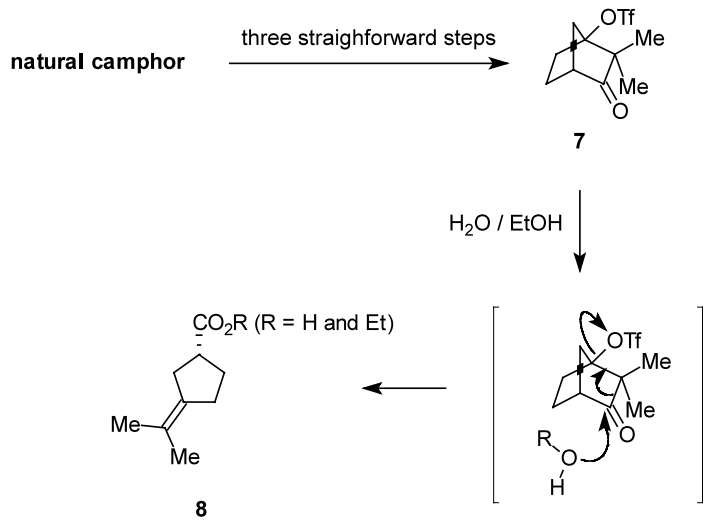
Thus, most of the reported syntheses of enantiopure sarkomycin are focused on the preparation of (−)-(*R*)- and (+)-(*S*)-sarkomycin methyl ester,[7e] (−)-cyclosarkomycin **6**,[6f–j] and (+)-cyclosarkomycin ***ent*-6**.[6e] In these syntheses, the desired enantiopurity is reached by means of: (a) an asymmetric process (generally an asymmetric Diels–Alder reaction employing a chiral auxiliary);[6f,6i,7e] (b) a kinetic resolution of a racemic mixture employing a chiral reagent,[6g] or an enzymatic biotransformation;[6j] and (c) a classical racemic resolution by diastereomer mixture formation and subsequent separation.[2a] Unfortunately, all these last processes have the disadvantage of a low overall yield (2–25%), which is generally due to a large number of individual steps (5–16), or the necessity to undergo a racemic mixture resolution.

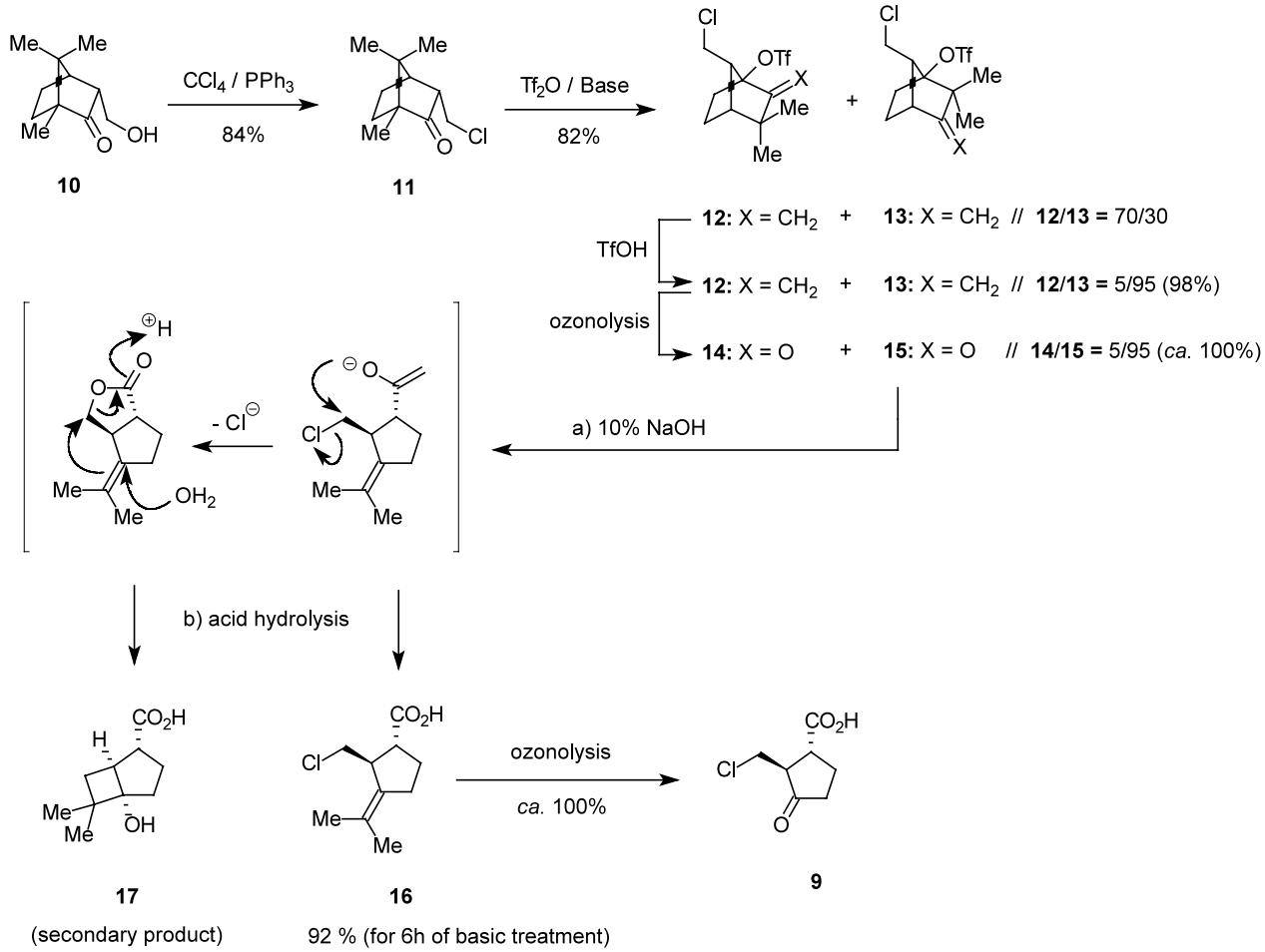
On the other hand, our laboratory has been engaged in a project directed toward the development of new general synthetic procedures towards cyclopentanoid carboxylic acids. Such procedures are based in the stereocontrolled fragmentation of a key bridgehead-substituted norbornane with convenient functionalization, which can be easily prepared from commercial available natural camphor.[8] These efforts have culminated in the establishment of new straightforward model procedures to interesting enantiopure cyclopentanoids such as jasmonoids,[8d] cyclopent-2-ene-, 3-methylenecyclopentane- and 3-oxocyclopentaneacetonitriles,[8b,8c] 3-oxocyclopentaneacetaldehydes,[8c] or C3-substituted cyclopent-2-eneacetic acids.[8a,8c,8e] In this sense, we have reported that the solvolysis of camphor-derived 2,2-dimethyl-3-oxonorborn-1-yl triflate **7** in aqueous ethanol takes place with stereocontrolled norbornane-ring opening to afford a mixture of 3-isopropylidenecyclopentane carboxylic acid (**8**, R = H) and the corresponding ethyl ester (**8**, R = Et) (Scheme 1). The accessible highly-stereoselective functionalization of camphor in several positions to generate analogs of ketotriflate **7**, subsequent described norbornane-ring opening (Scheme 1) and final isopropylidene ozonolysis could constitute a model procedure to enantiopure substituted 3-oxocyclopentane-carboxylic acids such as sarkomycin **1**.

As a result, we have now obtained (1*R*,2*S*)-2-chloromethyl-3-oxocyclopentanecarboxylic acid **9**, a promising precursor of sarkomycin **1**,[9] from natural (1*R*)-camphor, as described in Scheme 2. As starting functionalized camphor, we have used 3-*endo*-hydroxymethylcamphor **10**, which is easily obtained from (1*R*)-camphor in two straightforward steps, according to the procedure described by Gianini and Zelewsky,[10] with excellent yield and high diastereoselectivity. Treatment of **10** with excess of CCl_4/PPh_3 in acetonitrile affords the corresponding 3-*endo*-chloromethylcamphor **11** with 84% yield.[11] Reaction of chlorocamphor **11** with triflic anhydride (Tf_2O) takes place with Wagner–Meerwein rearrangement to give a mixture of the inseparable 7-*anti*-chloromethylnorborn-1-yl triflates **12** and **13** (**12**/**13** = 70/30, 82% yield).[12] The mixture of triflates **11** and **12** is submitted to TfOH-catalysed Nametkin rearrangement to obtain a new mixture of both triflates in which **13** predominates (**12**/**13** = 5/95, 98% yield).[13] This last mixture of methylenenorborn-1-yl triflates is ozonolyzed to the corresponding oxonorborn-1-yl triflates **14** and **15** in ca. quantitative yield.[14] The oxonorbon-1-yl triflates **14** and **15** obtained are easily separated by elution chromatography.[14] The time-controlled (6 h) treatment of 3-oxonorborn-yl triflate **15** with 10% NaOH affords cyclopentanoid **16** in 92% yield.[15] Bicycle **17** is detected as a secondary product for longer reaction times.[16] Finally, ozonolysis of isopropylidenecyclopentanoid **16** gives the desired chloroacid **9** in ca. quantitative yield.[17] Unfortunately, **9** proved to be not very stable, as many other sarkomycin precursors,[4,17] undergoing easily decomposition.

The stereocontrolled formation of bicycle **17** can be explained according to the mechanism described in Scheme 2. Thus, a γ-lactone could be generated from the initially formed cyclopentanecarboxylate intermediate for a long enough reaction time (Scheme 2). Such



Scheme 1. Stereocontrolled ring-opening of camphor-derived 3-oxonorborn-1-yl triflates.



Scheme 2. Preparation of **9** from natural camphor. A stereocontrolled approach to sarkomycin and related compounds.

undetected *trans*-lactone must be very unstable under the final acid treatment, undergoing an acid-catalysed cyclobutane-ring closing with synchronous lactone-ring opening (Scheme 2).

In summary, we have described the first stereocontrolled approach to enantiopure sarkomycin **1**, and related compounds, from commercially available natural camphor. The key-step of this process is an enantiospecific base-promoted ring opening of a 3-oxonorborn-1-yl triflate, which is conveniently functionalized at the C7 norbornane-position with a methylene precursor group. Subsequent ozonolysis yields an enantiopure 3-oxocyclopentanecarboxylic acid, which possesses the methylene precursor group at the adequate C2 cyclopentane position. The process occurs in only six individual steps with 59% overall yield. Unfortunately, the 3-oxocyclopentanocarboxylic acid **9** obtained proves unstable enough (a common characteristic of most of the sarkomycin derivatives)[4] to be a competitive sarkomycin precursor to the well-known cyclosarkomycin **6**.[6] We continue working in the herein established methodology for the preparation of other 3-oxocyclopentanecarboxylic acids analogous of **9**, which could be used as convenient sarkomycin precursors, but substituting the reactive chloromethyl group by other less reactive methylene group precursors.

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9. Enantiopure cyclopentanoid **9** could be an immediate precursor of sarkomycin **1** (by elimination of HCl).
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11. A solution of 1.0 mmol of **10**, 1.25 mol of PPh_3 and 1.25 mmol of CCl_4 in 10 mL acetonitrile was stirred at room temperature for 14 h. After that, the mixture was diluted with water, extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. After filtration and solvent evaporation, the obtained residue was diluted with hexane and treated carefully with 2 mL of H_2O_2 (110 vol.). The mixture was stirred for 24 h. After that, the mixture was filtrated to eliminate the formed $Ph_3P{=}O$. The filtrate was washed with water and dried over anhydrous $MgSO_4$. After a new filtration and hexane evaporation pure **11** was obtained as a colorless solid. Mp 28–30°C. $[\alpha]_D^{20}$+140 (0.09, CH_2Cl_2). ^{1}H and ^{13}C NMR, IR and MS spectra agree with the structure.
12. Over a solution of 10.0 mmol of **11** in 5 mL of triisobutylamine was slowly added 20.0 mmol of freshly distilled Tf_2O. The mixture was heated in a thermostatized bath at 40°C for 4 days. After that, the reaction mixture was allowed to cool down to room temperature and diluted with CH_2Cl_2. The mixture was washed with 20% HCl (3×20 mL), with saturated $NaHCO_3$ and with brine. After dried with anhydrous $MgSO_4$, filtration and solvent evaporation a liquid residue was obtained. After purification by elution chromatography (silica gel, hexane) a mixture of triflates **12** and **13** (**12**/**13** = 70/30 by ^{1}H NMR) was obtained as a colorless liquid in 82% yield. ^{1}H and ^{13}C NMR and IR of the obtained mixture, as well as the individual MS spectrum for each triflate obtained by

MS/GLC agree with corresponding structures. On a similar Wagner–Meerwein rearrangement see Ref. 8d.

13. Over a solution of 3.0 mmol of mixture **12**/**13** (70/30) in 25 mL of dry CH_2Cl_2, at −78°C and under an argon atmosphere, TfOH (3.0 mmol) was dropwise added. The mixture was stirred at −78°C for 30 min. After that, the mixture was treated with 4 mmol of triisobutylamine and allowed to warm up to room temperature. Then, the mixture was washed with 20% HCl (3×10 mL), saturated $NaHCO_3$ and brine. After dried with anhydrous $MgSO_4$, filtration and solvent evaporation, the obtained residue (a pale brown oil) was purified by elution chromatography (see Ref. 12), to obtain a new mixture of triflates **12** and **13** (**12**/**13** = 5/95 by ^1H NMR) in 98% yield.
14. Standard ozonolysis (ozone passed through a CH_2Cl_2 solution at −78°C, and subsequent reduction with Me_2S) was realized. After standard work up, both oxonorborn-1-yl triflates **14** and **15** (**14**/**15** = 5/95 by ^1H NMR) were separated by elution chromatography (silica gel, pentane/CH_2Cl_2 7:3) in ca. quantitative yield **14**: colorless solid. Mp 42–44°C. $[\alpha]_D^{20}$+12.5 (0.20, CH_2Cl_2). **15**: Colorless oil. $[\alpha]_D^{20}$+29 (0.30, CH_2Cl_2). ^1H and ^{13}C NMR, IR and MS spectra of both compounds agree with corresponding structures.
15. A dispersion of 1.5 mmol of triflate **15** in 15 mL 10% NaOH was stirred for 6 h. After that, the mixture was carefully acidulated with 10% HCl, and extracted with CH_2Cl_2. After drying with $MgSO_4$, filtration and solvent evaporation the obtained residue was purified by elution chromatography (silica gel, CH_2Cl_2/eter 7:3) to give pure **16** as a white solid (92% yield). **16**: Mp 46–48°C. $[\alpha]_D^{20}$ −8.8 (0.60, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 4.02 (ddd, J = 11.7 Hz, J = 10.3, Hz, J = 4.4 Hz, 1H), 3.10 (ddd, J = 13.5 Hz, J = 4.4 Hz, J = 1.7 Hz, 1H), 2.80–1.65 (m, 4H), 1.63 (s, 3H), 1.60 (s, 3H), 1.60–1.40 (m, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.0, 126.6, 125.6, 58.9, 52.9, 39.1, 29.9, 27.8, 20.1, 19.9 ppm. FTIR (CCl_4) 3018, 1713, 1215 cm^{-1}. MS z/e 166 ($M^{+\bullet}$–HCl, 22), 79 (100).
16. **17**: White solid. Mp 50–52°C. $[\alpha]_D^{20}$ +10 (0.10, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ 7.05 (br s, 2H), 2.86 (d, J = 7.9 Hz, 1H), 2.23–1.43 (m, 5H), 1.30 (s, 3H), 1.08 (s, 3H), 0.76 (dd, J = 8.4 Hz, J = 5.7 Hz, 1H), 0.43 (dd, J = 5.3 Hz, J = 4.4 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5, 71.2, 44.7, 37.7, 27.4, 27.3, 26.5, 26.1, 23.0, 10.6 ppm. FTIR (CCl_4) 3390, 3000, 1705, 1261 cm^{-1}. MS z/e 166 ($M^{+\bullet}$–18, 22), 121 (100).
17. Standard ozonolysis (see Ref. 14) was realized. After standard work up, **9** was obtained as a colorless oil in ca. quantitative yield. The product starts decomposing slowly after initial isolation. ^1H NMR (200 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 3.00 (dd, J = 15.2 Hz, J = 4.9 Hz, 1H), 2.69 (m, 1H), 2.40–2.26 (m, 2H), 2.11–1.50 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.2, 175.9, 55.2, 48.0, 47.7, 37.5, 24.1 ppm. It was not possible to measure the molecular rotation due to the instability of **9** (about a similar problem in other sarkomycin precursors, see Ref. 2a).