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Short Total Syntheses of Both the Putative and Actual Structures of the Clerodane Diterpenoid (±)-Sacacarin by Double Annulation

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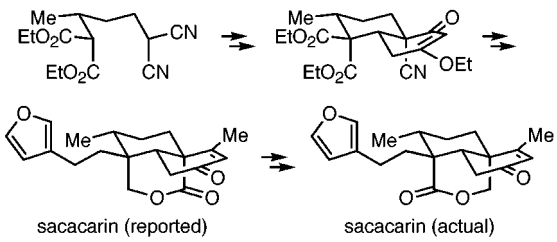
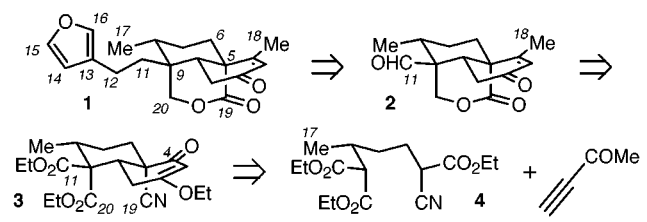
ABSTRACT



The putative structure of the naturally occurring clerodane diterpenoid (±)-sacacarin has been prepared in only 10 steps, six of which are C–C bond-forming steps, in a chemo-, regio-, and diastereoselective manner. The key part of the synthesis is the double annulation (double Michael, Pinner, and Dieckmann reaction) of a tethered carbon diacid and 3-butyn-2-one. A corrected structure for sacacarin is proposed, and the structure is proven by synthesis.

The clerodane diterpenoids constitute a large class of natural products, and many of them, especially those that are highly oxygenated, display potent insect antifeedant, antifungal, antibacterial, anticancer, and other desirable properties.[1] The biological activities and challenging structures of the clerodanes have stimulated much synthetic effort that has culminated in many total syntheses.[2] We have been investigating an efficient "double annulation" route to highly substituted and functionalized *trans*-decalins such as are found in the clerodanes.[3,4] We now demonstrate the utility of the double annulation with a short synthesis of the putative structure, **1** (Scheme 1), of the naturally occurring clerodane (±)-sacacarin.[5] Sacacarin is a minor component of the bark of a Brazilian tree that has "a history of safe use in folk medicine", especially for the treatment of digestive upset.[6] The oxygenated C(19) of **1** is a common feature among bioactive clerodanes,[1] but it is present in only a handful of the clerodanes synthesized thus far.[7] The synthesis of **1** described here is noteworthy for its brevity, its stereoselectivity, and its minimal use of protecting groups. The synthesis of **1** also reveals that the structure of sacacarin has been misassigned.[5] We suggest an alternative structure for saca-

Scheme 1



(1) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, 243. Rodríguez-Hahn, L.; Esquivel, B.; Cárdenas, J. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: New York, 1994; Vol. 63, p 107. Piozzi, F. *Heterocycles* **1994**, *37*, 603. Piozzi, F.; Bruno, M.; Rosselli, S. *Heterocycles* **1998**, *48*, 2185.

(2) Tokoroyama, T. *Synthesis* **2000**, 611.

(3) Grossman, R. B. *Synlett* **2001**, 13.

(4) Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867.

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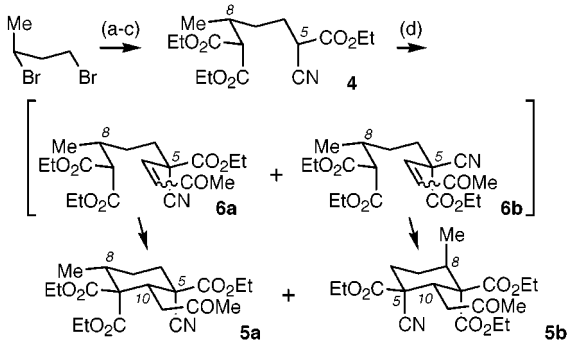
carin, and we prove its correctness by transforming **1** into this structure.

Compound **1** has several features that make it a particularly attractive target for a double annulation approach. Like most clerodanes, **1** has a *trans*-decalin ring system with quaternary centers at C(5) and C(9) and four contiguous stereocenters, but **1** is unusual in that both C(19) and C(20) are oxygenated whereas both C(6) and C(18) are unoxygenated. The double annulation provides *trans*-decalins with C(11), C(19), and C(20) in place as CN or CO_2Et groups,[8] making it appropriate for the synthesis of C(19)- and C(20)-oxygenated clerodanes such as **1**.

We planned to install C(12−16) of **1** by a Wittig reaction of aldehyde **2** (Scheme 1). The aldehyde and lactone groups of **2** would be derived from the cyano and ester groups of **3**, whereas C(18) of **2** would be introduced by addition of MeLi to the C(4) carbonyl group of **3**. The *trans*-decalin skeleton of **3** would in turn be prepared by a double annulation of "tethered diacid" **4** and 3-butyn-2-one that was selective for equatorial orientation of C(17).[3,9] In executing our synthesis, we desired to use the chemical information inherent in densely functionalized intermediates such as **4** to direct the necessary chemo-, regio-, and diastereoselective transformations to reach **1**, avoiding tedious protecting group manipulations wherever possible.

Tethered diacid **4** was easily prepared from 1,3-dibromobutane in three steps, on a large scale, and in good yield by a slight modification of methodology we reported a few years ago (Scheme 2).[10,11] The double Michael reaction of **4**

Scheme 2[a]



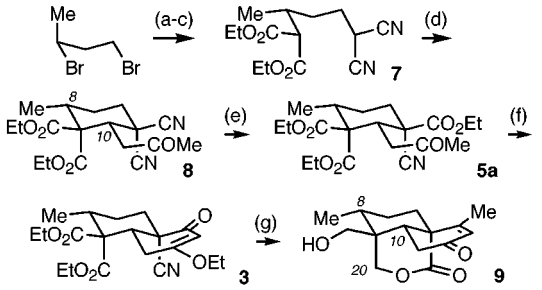
[a] (a) $Et_2C{=}C(CN)CO_2Et$, NaH, DMF, 82%; (b) $CH_2(CO_2Et)_2$, NaH, DMF, 86%; (c) O_3, CH_2Cl_2; EtOH, cat. TsOH, reflux, 91%; (d) HC≡CCOMe, *t*-BuOK, CH_2Cl_2, 0 °C, 66% (1:1 dr).

and 3-butyn-2-one catalyzed by 10 mol % *t*-BuOK in CH_2Cl_2 provided double Michael adducts **5a** and **5b** as a 1:1 mixture in 66% yield. Compounds **5a** and **5b** had the same C(5,10) relative stereochemistry (clerodane numbering), but they differed in their C(5,8) relative stereochemistry. This result was not terribly surprising; the first, intermolecular Michael reaction of **4** proceeded at the more acidic C(5), and because the existing C(8) stereocenter had no influence over the newly forming C(5) stereocenter, a 1:1 mixture of mono-Michael adducts **6a** and **6b** was formed. Nascent 1,3-diaxial interactions in the TSs leading from **6a**,**b** to **5a**,**b** then placed the acetonyl and axial CN groups exclusively in the equatorial positions, producing the same C(5,10) relative stereochemistry in **5a** and **5b**.

Compounds **5a** and **5b** were inseparable, and when the mixture was carried forward in the synthesis, the diastereomeric mixtures of later intermediates were also inseparable. We had found previously that certain kinetic double Michael adducts could be equilibrated to their thermodynamic isomers by a retro-Michael-Michael process,[8,11] but **5a** and **5b** underwent other reactions instead of equilibration. We did find conditions (10% KF·$2H_2O$, EtOH, rt) under which **6a** cyclized preferentially over **6b**, but the dr of **5a** obtained in this way was still only 5:1, and the yield was limited to about 25−30%. The failure of these strategies to provide **5a** or later intermediates in diastereopure form spurred us to design a new route that avoided the generation of a stereocenter in the first Michael reaction.

Tethered diacid **7** (Scheme 3), prepared in the same way

Scheme 3[a]



[a] (a) $Et_2C{=}C(CN)_2$, NaH, DMF, 59%; (b) $CH_2(CO_2Et)_2$, NaH, DMF, 85%; (c) O_3, CH_2Cl_2; EtOH, cat. TsOH, reflux, 88%; (d) $Me_3SiC{\equiv}CCOMe$, 15 mol % KF·$2H_2O$, *t*-BuOH, rt, 66% (60:1 dr); (e) EtOH, dry HCl; conc. aq. HCl, DME, 99%; (f) NaOEt, EtOH, reflux; cat. TsOH, EtOH, $C_6H_6-H_2O$, reflux, 90%; (g) MeLi, THF, −78 °C; Me_3SiCl; $LiAlH_4$, 0 °C; quench, filter through Celite, evaporate; conc. aq. HCl, reflux, 62%.

as **4**, differs from **4** in that neither of its acidic centers is stereogenic. Upon double Michael reaction of **7** and 3-butyn-2-one (prepared in situ from 4-trimethylsilyl-3-butyn-2-one)[12]

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(6) Maciel, M. A. M.; Pinto, A. C.; Arruda, A. C.; Pamplona, S. G. S. R.; Vanderlinde, F. A.; Lapa, A. J.; Echevarria, A.; Grynberg, N. F.; Côlus, I. M. S.; Farias, R. A. F.; Costa, A. M. L.; Rao, V. S. N. *J. Ethnopharmacology* **2000**, *70*, 41.

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(8) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.

(9) The term "tethered diacid" refers to compounds such as **4** that consist of two carbon acids connected by a tether.

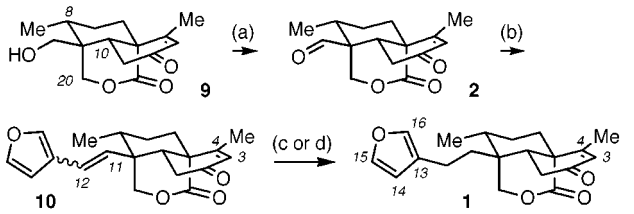
catalyzed by 15 mol % KF·$2H_2O$ in *t*-BuOH, adduct **8** is obtained in 5:1 dr, but nearly diastereopure **8** crystallizes from the reaction mixture (before and after workup) in 66% yield and 60:1 dr. The stereochemistry of **8** is confirmed by X-ray analysis. In contrast to the previous double Michael reaction, the stereochemistry-determining step leading to **8** is the second, intramolecular Michael reaction, and it occurs preferentially from a conformation in which both the C(8) methyl group and the nascent C(10) acetonyl group are pseudoequatorial. The 5:1 dr of the crude **8** is close to the thermodynamic dr of 5.6:1 that is roughly calculated from accepted values for gauche and 1,3-diaxial interactions in substituted cyclohexanes,[13] as would be expected from a kinetically controlled reaction with a product-like TS.

Treatment of **8** with dry HCl in absolute EtOH and then 6 N aqueous HCl in DME provides diastereopure cyano triester **5a** in 99% yield. Only the equatorial CN group in **8** participates in the Pinner reaction, presumably because of steric encumbrance of the axial CN group. We have observed similarly high reactivity of an equatorial CN group as compared to an axial one in intramolecular reductive amination reactions of several double Michael adducts.[8,14]

A Dieckmann reaction of **5a** and enol etherification provides *trans*-octalone **3** in 90% yield.[8] (The other 10% of the material is the transposed β-ethoxyenone, which is easily removed chromatographically and can be isomerized to 90% **3** by resubjection to the etherification conditions.) Compound **3** is treated with exactly 1 equiv of MeLi to add to the ketone, then Me_3SiCl to quench the nascent alkoxide, and then $LiAlH_4$ to reduce the esters.[15] After quenching, filtration through Celite, and evaporation, concentrated aqueous HCl is added, and the mixture is brought to reflux. The acid treatment hydrolyzes the γ-silyloxy enol ether to the enone and catalyzes lactonization to provide tricyclic **9** in 62% yield, thus completing the differentiation of the five functional groups of double Michael adduct **8**. The ^{1}H NMR spectrum of **9** shows that one H(20) atom participates in W-coupling with H(8) and the other with H(10). These data confirm the stereo- and regiochemistry of the Pinner and Dieckmann reactions, as no other isomer would be expected to show these spectral features.

The final steps in the synthesis of **1** convert the very hindered hydroxymethyl group of **9** to a 2-(3-furyl)ethyl group (Scheme 4). The CH_2OH group of **9** is oxidized with NMO and catalytic TPAP to give aldehyde-lactone **2** in 77% yield. A Wittig reaction of **2** with (3-furyl)CH=PPh_3[16] in

Scheme 4[a]



[a] (a) NMO, cat. TPAP, 4 Å MS, CH_2Cl_2, 77%; (b) (3-furyl)-CH=PPh_3, DMPU, 70% **10** (4:1 *Z*:*E*); (c) $HOCH_2CH_2OH$, cat. TsOH, $C_6H_6-H_2O$; 1 atm H_2, 10% Pd/C, EtOAc, 1 h; 1 N HCl, THF, 28% **1**, 44% 13,14,15,16-tetrahydro-**1**; (d) $HOCH_2CH_2OH$, cat. TsOH, $C_6H_6-H_2O$; 1000 psi H_2, Lindlar catalyst, EtOAc, 12 h; 1 N HCl, THF, 90% 7:2:1 mixture of **1**, **10**, and 3,4-dihydro-**1**.

DMPU provides alkene **10** in 70% yield (4:1 *Z*/*E*). This reaction fails in THF, perhaps because of solubility issues. The last step, reduction of the C(11,12) π bond, turns out to be difficult to accomplish selectively in the presence of the less hindered, equally reactive furan and C(3,4) π bonds. One solution—ketal formation to protect the C(3,4) π bond, hydrogenation of the C(11,12) π bond over Pd/C, and ketal hydrolysis—affords **1**, but in only 28% yield; 13,14,15,16-tetrahydro-**1** is also obtained in 44% yield, although it is easily separated. Another solution, hydrogenation of the ketal over Lindlar catalyst (1000 psi, 12 h) instead of Pd/C, avoids the formation of tetrahydro-**1**, instead giving a 90% yield of a 7:1:2 mixture of **1**, 3,4-dihydro-**1**, and **10**. Unfortunately, these compounds are inseparable, and further hydrogenation gives larger proportions of 3,4-dihydro-**1**. Note that the protection of the enone in either of these sequences constitutes the *only* protection in the entire synthesis of **1**.

We are confident that a better-yielding route from **2** to **1** can be found, but our drive to find it is diminished by the fact that the NMR spectra of **1** do not match those of sacacarin.[5] Most notably, in $CDCl_3$ the two lactone H atoms of sacacarin resonate at δ 4.43 (s), whereas those of **1** appear at δ 4.00 (dd, 12.6 and 1.0 Hz) and 4.39 (dd, 12.6 and 0.7 Hz). Also, the H(18) methyl group resonates at δ 1.97 in sacacarin, whereas it appears at δ 2.26 in **1**. The upfield shift

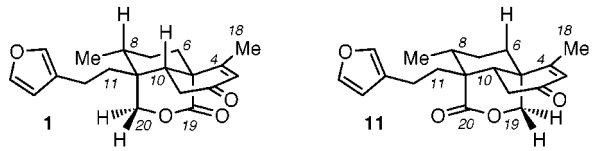


Figure 1. The originally assigned (left) and corrected (right) structures of sacacarin.

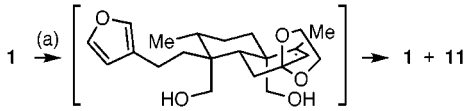
of H(18) in sacacarin as compared to **1** is best explained by structure **11** (Figure 1): C(18) is further from the deshielding

(10) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235.
(11) Grossman, R. B.; Rasne, R. M.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7173.
(12) 4-Trimethylsilyl-3-butyn-2-one is considerably safer, less expensive, and easier to prepare than 3-butyn-2-one. The double Michael reaction that uses 3-butyn-2-one generated in situ from 4-trimethylsilyl-3-butyn-2-one is therefore much more convenient than the one that uses pure 3-butyn-2-one. Komarov, N. V.; Yarosh, O. G. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 247. Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45.
(13) Carroll, F. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole Publishing Co.: Pacific Grove, CA, 1998.
(14) Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178.
(15) The Me_3SiCl maintains the solubility of the intermediate(s) after the $LiAlH_4$ is added.
(16) van Altena, I. A.; Miller, D. A. *Aust. J. Chem.* **1989**, *42*, 2181.

lactone carbonyl group in **11** than it is in **1**. In fact, in their paper describing sacacarin's isolation and structure determination,[5] Maciel et al. consider both **1** and **11** as possible structures for sacacarin. Their assignment of **1** as the structure rests on the observation of a three-bond coupling between "C(11)" and "H(20)" in the COLOC (long-range heteronuclear coupling) NMR spectrum of sacacarin. However, the large amount of overlap in the ^{1}H and ^{13}C NMR spectra of sacacarin makes the resonance assignments problematic. We believe that Maciel et al.'s "C(11)" and "H(20)" resonances actually arise from C(6) and H(19).[17] Structure **11** is also more consonant with the structures of previously isolated C(19,20)-lactone-bridged clerodanes, which have the carbonyl group at C(20).[5]

We have transformed **1** into sacacarin to confirm the new structural assignment (Scheme 5). Compound **1** is protected as its ketal, reduced with $LiAlH_4$, oxidized with NMO and catalytic TPAP, and deprotected to give a chromatographically separable 2.5:1 mixture of **1** and **11** (68% yield). The spectral features of the synthetic **11** are identical to those of sacacarin.[5] This sequence is clearly not a viable route to large amounts of **11**, but it unambiguously proves the correct structure of sacacarin.

Scheme 5[a]



[a] (a) $HOCH_2CH_2OH$, cat. TsOH, $C_6H_6-H_2O$; $LiAlH_4$, THF; NMO, cat. TPAP, 4 Å MS, CH_2Cl_2; 1 N HCl, THF, 19% **11**, 49% **1**.

The synthesis of **1** described here has several noteworthy features. Only 10 steps, six of which are C−C bond-forming steps, are used to prepare this complex, 20-carbon "natural product". The five carbonyl and cyano groups of double Michael adduct **8** are elaborated chemo-, regio-, and diastereoselectively using the stereochemical information inherent in the intermediates. The four contiguous stereocenters in **1** are controlled by the single stereocenter in 1,3-dibromobutane.

Our synthesis of **1** is also quite unwasteful for a synthesis of a complex "natural product". Only one brief protection of an enone with ethylene glycol is required. Triphenylphosphine oxide is the only waste product that is not removed upon rotary evaporation or aqueous workup.[18] Only three intermediates (**3**, **9**, and **10**) and the product **1** are purified by flash chromatography, and even these compounds are crystalline. Also, the synthesis requires only inexpensive and widely used reagents. On the other hand, the poor regioselectivity of the hydrogenation step remains a problem that must be addressed in future synthetic endeavors.

Our syntheses of **1** and **11** establish the correct structure of sacacarin. Although it has turned out that **1** is not a natural product, our methodology is clearly adaptable to the synthesis of other, naturally occurring C(19)-oxygenated clerodane diterpenoids. Further investigations in this area, including asymmetric routes to clerodanes and other diterpenoids, will be described in due course.

Acknowledgment. We thank Dr. Sean Parkin for the X-ray analysis of **8** and Prof. Maria Aparecida M. Maciel for sharing the original spectra of sacacarin with us. We also thank the NSF (CAREER award CHE-9733201) and the NIH (GM1002-01A1) for their support of this work. NMR instruments used in this research were obtained with funds from NSF's CRIF program (CHE-997841) and the University of Kentucky's Research Challenge Trust Fund.

Supporting Information Available: Experimental details for the preparation and full characterization of compounds **1**−**5** and **7**−**11**, and data from X-ray crystallographic analysis of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) New 600 MHz spectra of sacacarin confirm both the reassigned structure and the origin of the misassignment. Maciel, M. A. M. Personal communication.

(18) The other stoichiometric organic waste products are ethyl acetate and propionate (step 3), Me_3SiOR (steps 4 and 7), ethanol (steps 6 and 7), *N*-methylmorpholine (step 8), and ethylene glycol (step 10). Of course, solvent waste must also be considered. We use the polar aprotic solvents DMF (steps 1 and 2) and DMPU (step 9); the former is removed by vacuum distillation prior to aqueous workup and can be reused. We do also use the conventional "problem solvents" CH_2Cl_2 (step 3) and benzene (steps 6 and 10); we have not yet sought alternatives to them at this stage of our research.