acrylate structure in **5**. In addition, we anticipate that thermal[11,12] and organometallic[13] reactions of the substituted cyclopropenone ketals (e.g., **3**) will provide exciting new fields of future research.

(11) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695 and references therein.
(12) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.*, in press.
(13) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297.

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Supplementary Material Available: Physical properties of cyclopropenones (7 pages). Ordering information is given on any current masthead page.

Synthesis and Absolute Configuration of (−)-Furodysinin. New Transformations of Camphor Derivatives

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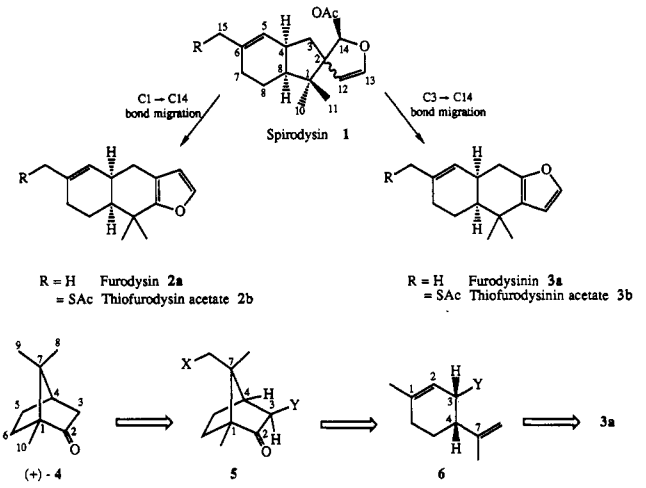
Summary: The synthesis of (−)-furodysinin ((−)-**3a**) has been accomplished in five steps from (+)-π-bromocamphor (**7**) and has allowed assignment of the absolute configuration of a number of marine furanosesquiterpenes produced by sponges of the genus *Dysidea*.

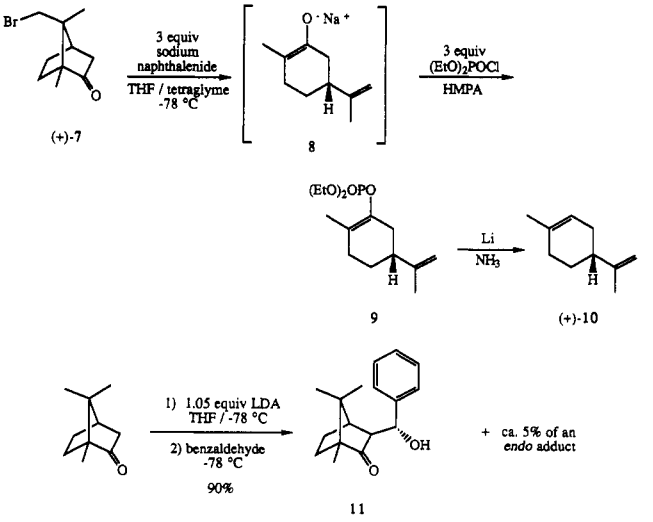
Sir: Tropical sponges of the family Dysideidae are sources of a wide variety of secondary metabolites including polybrominated diphenyl ethers, amino acid derived substances, and a variety of terpenes.[1,2] In particular, the Indo-Pacific sponge *Dysidea herbacea* elaborates furanosesquiterpenes of many skeletal types.[3] Among these are the tricyclic compounds shown in Scheme I that were originally isolated and described by Wells and co-workers in 1978.[4] Furodysin (**2a**), furodysinin (**3a**) and their thioacetyl analogues have been shown to arise by solvolysis and cationic rearrangement of spirodysin (**1**), a cometabolite found in this species. The relative configurations of the compounds were determined spectroscopically and by use of X-ray crystallography. Although the absolute configurations of **1–3** have not been determined, it is interesting that both enantiomers of **3a** have been detected in the same sponge genus from sources only 1500 miles apart.[5,6] It is reasonable to assume that **2** and **3** arise in the sponge from **1**. In a general approach to metabolites **2–3** among others, we have expanded the versatile chemistry of camphor[7] to achieve a concise synthesis[8] of (−)-furodysinin from (+)-camphor (**4**) thus establishing the absolute configuration of this series of sponge metabolites.

Our general strategy (Scheme I) was to derivatize camphor prior to cleavage of the C1–C7 bond, which establishes the eventual cis junction of the bicyclo[4.4.0] ring system. Two model studies established the viability of our approach (Scheme II). In the first model, a fragmentation of the bicyclo[2.2.1] ring system[9] was achieved by treating (+)-9-bromocamphor (**7**) with 3 equiv of sodium naphthalenide in THF at −78 °C, presumably resulting in the regiospecifically generated enolate **8**, which was trapped with diethyl chlorophosphate to give the enol phosphate **9** in 80% yield. Dissolving metal reduction of **9** led to (+)-limonene (**10**) in 80% yield, thus allowing camphor to be used as a six-membered chiral pool element. The exo alkylation of camphor at the 3-position must also be

Scheme I



Scheme II



achieved to utilize this process for the production of **2–3**. In a surprising development, the desired exo alkylation of

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(1) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1–34.
(2) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551–598.

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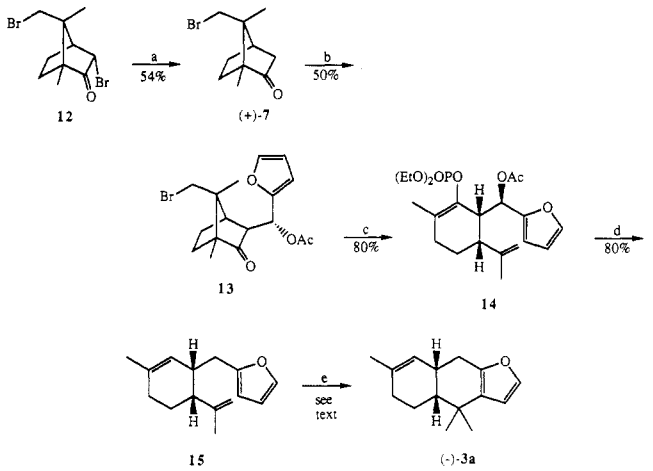
Scheme III[a]



[a] Reagents: (a) Zn/HOAc; (b) 1.05 equiv of LDA/THF/−78 °C, 1.5 h, then 1.0 equiv of 2-furaldehyde, −78 °C, 10 min; (2) Ac_2O/DMAP/Et_3N, 25 °C, 10 min; (c) 3 equiv of sodium naphthalenide/THF/tetraglyme; quench with 1.5 equiv of $(EtO)_2POCl$/−78 to −40 °C; (d) 10–20 equiv of Li/NH_3/−78 °C; (e) 1.5 equiv of $Hg(NO_3)_2/CH_2Cl_2$, 0 °C → 25 °C, 4 h; then $NaBH_4$/aqueous NaOH.

the enolate of camphor can be easily accomplished by aldol reaction, leading to predominantly exo selectivity. For example, treatment of camphor with 1.05 equiv of LDA in THF at −78 °C followed by quenching of the enolate with benzaldehyde at −78 °C for 5 min results in the formation of a single exo adduct (**11**) in >90% yield along with approximately 5% of a single endo adduct. Similar exo diastereoselectivity is observed with other aldehydes but not with alkyl halides.[10] We are investigating these phenomena further to uncover the origin of this unexpected behavior.[11] These models provided the information needed to proceed with the synthetic plan (Scheme III).

(+)-9-Bromocamphor (**7**) can be prepared in multihundred gram quantities from (+)-camphor in three steps.[12] An intermediate in this process is the commercially available[13] (+)-3-*endo*-9-dibromocamphor (**12**), which can be reduced with Zn/HOAc to provide optically pure (+)-**7**. Treatment of **7** with LDA/THF at −78 °C for 1.5 h followed by the addition of 2-furaldehyde at −78 °C gave a 1:2.5 mixture of a single endo and a single exo adduct.[14] This mixture was acetylated under standard conditions and the desired major isomer separated by a single recrystallization from 2-propanol to give the exo adduct acetate **13** in 50% overall yield. Thus in a single step, all 15 carbons have been assembled and both stereocenters are set. Cleavage of the C1–C7 bond could be accomplished by treating **13** with 3 equiv of sodium naphthalenide in THF/tetraglyme at −78 °C. Quenching of the resulting enolate with 1.5 equiv of diethyl chlorophosphate and warming to −40 °C provides the enol phosphate **14** in 80% yield. Reductive cleavage of both the phosphate and acetoxy groups was achieved by excess lithium in ammonia at −78 °C to provide the limonene derivative **15**. Cyclization of this substance using $Hg(NO_3)_2$ in CH_2Cl_2 followed by a reductive workup provides a mixture of cyclized and uncyclized products containing (−)-**3a** in 50–70% yield. Chromatography on silica provides a fraction of optically pure (−)-furodysinin (**3a**) in ca. 10% yield, which is spectroscopically identical, although opposite in rotation, with a sample of natural (+)-furodysinin.[15] Rechromatography of other fractions yields additional amounts of (−)-**3a**.[16] The assignment of the natural configurations of (+)-**1**–**3**[17] can now be assigned as shown in Scheme I.

In summary, a five-step synthesis of optically pure (−)-furodysinin has been accomplished starting from (+)-9-bromocamphor, establishing the absolute configuration of compounds in this series. The route in adaptable to the production of both furodysin (**2a**) and the thioacetate derivatives **2b** and **3b**. Studies are underway in this area and will be reported in due course.

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Supplementary Material Available: Listing of detailed procedures and spectral data for the synthetic sequence as well as raw NMR spectra of natural and synthetic furodysinin (8 pages). Ordering information is given on any current masthead page.

(3) (a) Guella, G.; Mancini, I.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1985**, *68*, 1276–1282. (b) Guella, G.; Guerriero, A.; Pietra, F. *Ibid.* **1985**, *68*, 39–48; also see ref 1 and 2.

(4) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4949–4950 and 4951–4954.

(5) Private communication from Prof. Philip Crews.

(6) (−)-Furodysinin has also been found in *Dysidea tupha* collected in the East Pyrenean Mediterranean. See ref 3a.

(7) Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253–289.

(8) Racemic furodysinin has previously been synthesized in approximately 12 steps by Hirota, H.; Kitano, M.; Komatsubara, K.; Takahashi, T. *Chem. Lett.* **1987**, 2079–2080.

(9) This has previously been achieved either in very low yield or proceeds with concommitant reduction of the carbonyl group. See: Hamon, D. P. G.; Taylor, G. F.; Young, R. N. *Synthesis* **1975**, 428–430. Gustafson, D. H.; Erman, W. F. *J. Org. Chem.* **1965**, *30*, 1665–1666. Baker, K. M.; Davis, B. R. *Tetrahedron* **1968**, *24*, 1655–1662.

(10) Unpublished results from this laboratory. For a summary in this area, see ref 7.

(11) While the predominant endo addition of electrophiles to the camphor enolate is well precedented, the nearly exclusive exo aldol reactions are unexpected from both a kinetic and a thermodynamic point of view. For a further discussion of enolate anion chemistry of the bicyclo[2.2.1] ring system, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 45–50.

(12) Of the various procedures in the literature (contained in ref 7), the best for large-scale (>100 g) work in our hands is that of D. Lawrence, Ph.D. Dissertation, UCLA, 1982.

(13) Available from the Aldrich Chemical Co., Milwaukee, WI.

(14) In general, we have found that the aldol reaction between camphor and aldehydes gives rise predominantly to a single major exo adduct and a single minor endo adduct (unpublished work of Mr. Mohamad R. Agharahimi). These stereochemistry at C-3 of these adducts (camphor numbering) is easily determined by ^1H NMR decoupling, with the exo adducts exhibiting a coupling constant of ca. 0 Hz between the hydrogens at C_3 and C_4 while the endo isomers possess a coupling of about 3–4 Hz. The full stereochemistry of **13** was assigned by decoupling and by analogy with compound **11**, the structure of which was determined by X-ray crystallography (details to be published in the full account of this work).

(15) (+)-Furodysinin has a reported $[\alpha]_D$ = +64° (Wells) and (−)-furodysinin $[\alpha]_D$ = −47° (Pietra). Our synthetic sample exhibits $[\alpha]_D$ = −54° (c = 0.5, $CHCl_3$).

(16) While the crude cyclization product appears to contain (−)-**3a** as the major component, large losses are incurred in the reaction workup and chromatographic separation of the natural product.

(17) This refers to the metabolite series isolated and described by Wells in ref 4.