Synthesis and Absolute Configuration of the Antiparasitic Furanosesquiterpenes (-)-Furodysin and (-)-Furodysinin. Camphor as a Six-Membered Ring Chiral Pool Template

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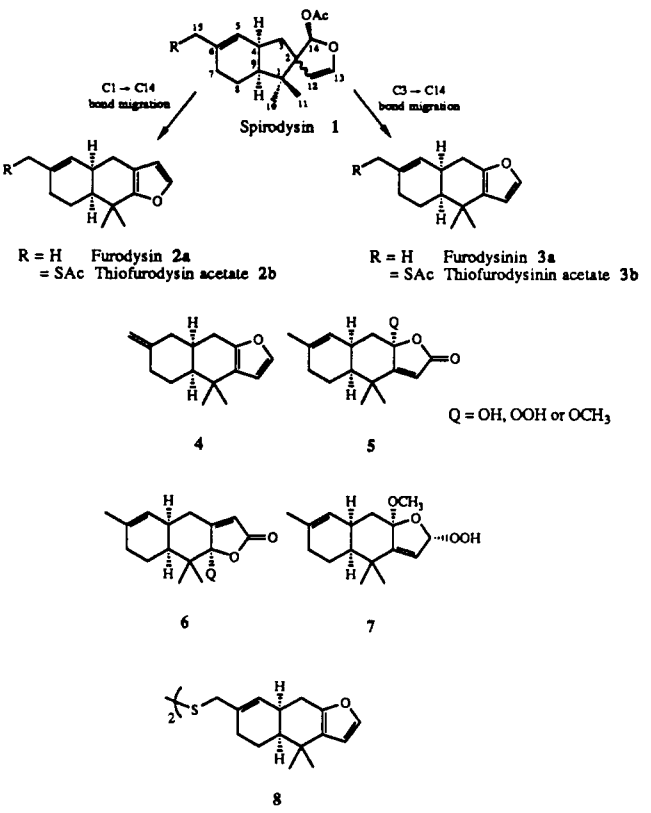
The syntheses of (-)-furodysin ((-)-**2a**) and (-)-furodysinin ((-)-**3a**) in four steps starting from (+)-9-bromocamphor (**18**) has been accomplished, thus establishing the absolute configuration of these and related metabolites. This was made possible by the unexpected exo selectivity in the aldol condensation of camphor-like enolates with aldehydes. This has been found to be a general phenomenon in the camphor system. Further, anionic fragmentation of the C1–C7 bond of camphor derivatives has allowed access to synthetic intermediates containing functionalized six-membered rings, thus opening up avenues from camphor to a new class of chiral pool elements not currently available from chiral pool substances.

Furanosesquiterpenes are ubiquitous metabolites found in a variety of marine invertebrates. In particular, pantropically occurring sponges of the genus *Dysidea* (family Dysideidae) elaborate furanosesquiterpenes of many skeletal types.[1] Substances in these categories frequently exhibit antibiotic activity and have been the subjects of substantial synthetic activity in recent years.[2] Notable in this regard are the tricyclic compounds shown in Scheme I, which were originally isolated and described by Wells and co-workers in 1978.[3] Furodysin (**2a**) and furodysinin (**3a**) are the parent compounds of two isomeric series of metabolites found in several species of *Dysidea*. The relative configurations of **2a** and **3a** were determined spectroscopically and by use of X-ray crystallography. Additionally, the unusual thioacetyl analogues **2b** and **3b** have been found to co-occur in *Dysidea* species.[3,4] Frequently these metabolites are accompanied in nature by oxidized furan analogues such as **5–7**.[4c,5] Interestingly, both enantiomers of some of the metabolites have been found in various *Dysidea* species. For example, Wells originally described the (+) isomers of **2a** and **3a** (absolute configuration unknown at the time) originating from an Australian variety of *D. herbacea*, while Pietra[1b] has described (-)-**3a** from Mediterranean samples of *D. tupha*. Curiously, Crews[4c] has reported both (-)-**3a** and (-)-**3b** from *D. herbacea* collected in Fiji. The two isomeric series (hereafter referred to as dysins and dysinins) are probably biogenetically derived from spirodysin (**1**, R = H), a co-metabolite of *D. herbacea*. Treatment of **1** with BF_3 etherate results in cationic rearrangement producing both **2a** and **3a** in a 1:1 ratio.[3] Prior to our work, the absolute configuration had not been determined for any of the metabolites in this series.

Until recently, no significant biological activity of any of these metabolites other than moderate antibiotic and antifeedant activity[5] had been uncovered. However, Crews[4c] has recently reported that anthelmintic screening of crude *Dysidea* extracts and purified metabolites against parasitic stages of *Nippostrongylus brasiliensis* revealed significant activity.

In a general approach to metabolites **2** and **3** among others, we have expanded the versatile chemistry of camphor to achieve a concise synthesis of both (-)-furodysin ((-)-**2a**) and (-)-furodysinin ((-)-**3a**) from (+)-π-bromocamphor (**18**) in four steps,[6] thus establishing the absolute configuration of this series of sponge metabolites.[7] In this note, we wish to detail our results in this area.

Scheme I. Metabolites of *Dysidea herbacea* and Related Species



† Wayne State University.
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(1) For summaries, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1–34. Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551–598. (b) Guella, G.; Mancini, I.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1985**, *68*, 1276–1282. (c) Guella, G.; Guerriero, A.; Pietra, F. *Ibid.* **1985**, *68*, 39–48.

(2) (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988. (c) Naispuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. I* **1979**, 2776. (d) Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1580. (e) Liotta, D.; Ott, W. *Synth. Commun.* **1987**, *17*, 1655. (f) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685. (g) Kurth, M. J.; Soares, C. J. *Tetrahedron Lett.* **1987**, *28*, 1031. (g) Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 491. (h) Nakano, T.; Maillo, M. A. *Synth. Commun.* **1981**, *11*, 463. (i) Baker, R.; Sims, R. J. *Tetrahedron Lett.* **1981**, *22*, 161. (j) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 105.

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

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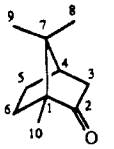
General Approach

Camphor (9) is a flexible chiral substance, easily derivatized at any of its 10 carbons.[8] Functionalization at the



9 (+)-camphor

apparently unactivated positions is possible by virtue of the notorious cationic rearrangements to which bicyclo[2.2.1] ring systems are prone. As a chiral pool element, the main usage of camphor has been as a template for construction of stereogenically pure five-membered ring intermediates by cleavage of the C1–C2 or C2–C3[9] bonds. Additionally, the entire carbon skeleton of **9** has been incorporated intact into α-santalene,[10] α-santalol,[11] isoepicampherenol,[12] campherenone,[13] camphrerenol,[12] and copacamphor.[12] Although limonene and carvone are useful six-membered ring chiral pool elements, derivatization of these molecules is difficult due to the moderate regio- and stereoselectivity of their C–C and C–heteroatom bond-forming reactions. Limonene is especially unsatsifactory in this regard, as evidenced by a recent review.[14] If one could fragment either the C1–C7 or C4–C7 bond of **9**, a new set of chiral pool elements could be accessed.[15] When combined with the easy derivatization of **9**, a large number of substituted six-membered ring synthons are possible. Our synthetic studies were prompted by the structural relationship of the dysins and dysinins to camphor. Syntheses of furodysin and furodysinin were designed within the context of this framework.

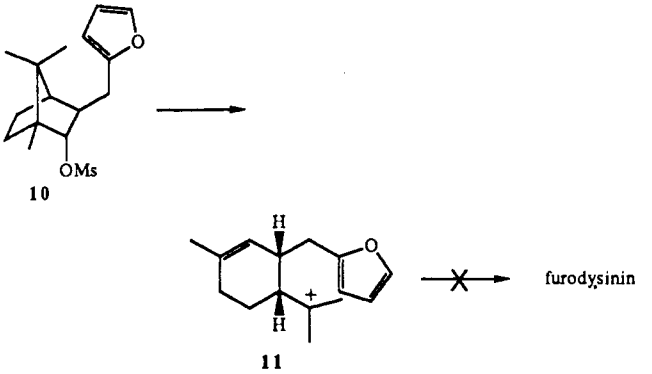
Our initial approach involved cleaving the C1–C7 bond in a cationic process by solvolysis of an endo leaving group at the 2-position (**10**) to the cation **11**, which could potentially cyclize onto the furan ring, producing the parent furodysinin (or furodysin) in one step from **10**. Substrate **10** and derivatives were produced in low overall yield by nonstereoselective alkylation of the camphor enolate with 2-furyl bromide followed by reduction with Na/NH_3 to predominantly the endo alcohol and subsequent mesylation. Treatment of **10** under ionizing conditions gave

Table I. Adduct Ratios from the Reaction of the Camphor Enolate with Aldehydes

aldehyde RCHO, R	yield of adducts (%)[a]	exo/endo (14:15)[b]
Me	82	3.3/1.0
Et	64	3.2/1.0
i-Pr	63	3.1/1.0
t-Bu	80	7.6/1.0
Ph	85	11/1.0
$PhCH_2$	91	1.6/1.0
2-furyl	89	4.4/1.0

[a] Yields refer to isolated adduct mixtures ≥95% spectroscopically pure. [b] Ratios determined by ^1H NMR integration.

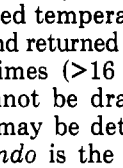
bicyclic solvolysis products or underwent uncontrolled solvolysis to more than 10 products, none of which were olefinic or contained a furan ring. This is not surprising



10 11

in light of the notorious acid sensitivity of electron-rich furan rings. Since several aspects of this approach were dissatisfying, we decided to examine two facets of the problem in greater depth. These were the cleavage of the C1–C7 bond by a carbanionic process and control of C3 alkylation reactions.

Alkylation of bicyclo[2.2.1]octan-2-ones has been studied in detail by Money among others.[16] Kinetic alkylation of the camphor enolate with methyl iodide gives predominantly the exo methylated product **12**-*exo*. This contrasts with conventional wisdom in which reagents normally approach the camphor carbonyl from what is thought to be the less hindered bottom face. Despite these reports, we found that benzyl bromide and 2-furyl bromide, both of which are more sterically demanding than methyl iodide, react to give primarily endo alkylation products. These reactions required temperatures around 0 °C to proceed at useful rates and returned 30–60% starting material after long reaction times (>16 h). Reliable stereochemical conclusions cannot be drawn here, however, since the product ratios may be determined thermodynamically. Note that **12**-*endo* is the thermodynamic isomer of 3-methylcamphor as determined by equilibration.[17]



12 ***exo*** (kinetic product)
12 ***endo*** (thermodynamic product)

Fortunately, we found early on that reaction of the camphor enolate with 2-furaldehyde (eq 1, R = 2-furyl) generates predominantly one exo adduct (major) and one endo adduct (minor). Other isomers could not be detected

(4) (a) Capon, R. J.; MacLeod, J. K. *J. Nat. Prod.* **1987**, *50*, 1136. (b) Guella, G.; Mancini, I.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1985**, *68*, 1276. (c) Horton, P.; Inman, W.; Crews, P. *J. Nat. Prod.* **1990**, *53*, 143.

(5) Carte, B.; Kernan, M. R.; Barrabee, E. B.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 3528.

(6) Richou, O.; Vaillancourt, V.; Faulkner, D. J.; Albizati, K. F. *J. Org. Chem.* **1989**, *54*, 4729.

(7) Both furodysin and furodysinin have been synthesized in racemic form in approximately 12 steps. See: Hirota, H.; Kitano, M.; Komatsubara, K.; Takahashi, T. *Chem. Lett.* **1987**, 2079–2080.

(8) For an excellent review of camphor chemistry, see: Money, T. *Nat. Prod. Rep.* **1985**, 2, 253.

(9) For a convenient table of references to these cleavages, see ref 8, sections 8.1 and 8.2.

(10) Kamat, S. Y.; Chakravarti, K. K.; Bhattacharya, K. K. *Tetrahedron* **1967**, *23*, 4487. Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755.

(11) Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314.

(12) Eck, C. R.; Hodgson, G. L.; MacSweeney, D. F.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. I* **1974**, 1938.

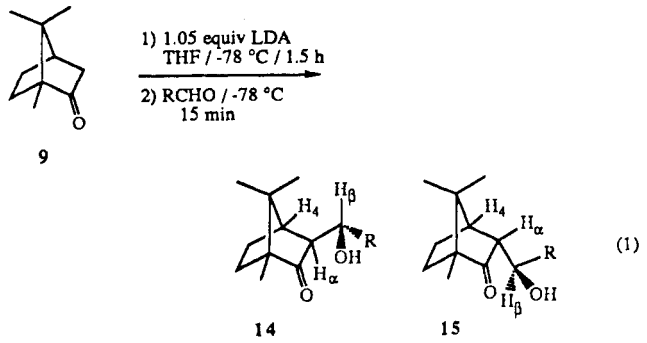
(13) Cachia, P., Piper, S. E.; T. Money, unpublished results.

(14) Thomas, A. F.; Bessiere, Y. *Nat. Prod. Rep.* **1989**, *6*, 291.

(15) The C1–C7 bond has been fragmented previously, either in low yield or with poor chemospecificity. 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.

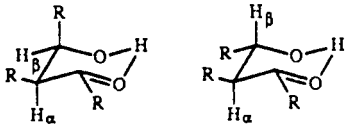
(16) For a discussion of this topic, as well as leading references, see ref 8, section 7.

(17) Hutchinson, J. H.; Money, T. *Can. J. Chem.* **1984**, *62*, 1899.



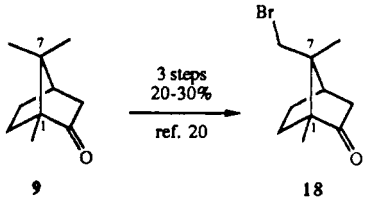
spectroscopically or by analytical HPLC on silica. We investigated this phenomenon briefly and found that all aldehydes examined exhibited exo selectivity, observing in each case one major exo adduct and one minor endo adduct. The results are shown in Table I. As can be seen, the exo/endo ratio is only slightly dependent on the steric bulk of the aldehyde in the alkyl series, while benzaldehyde gives the highest exo/endo ratio. The origin of this unexpected stereoselectivity is being studied further and will be the subject of a future report.

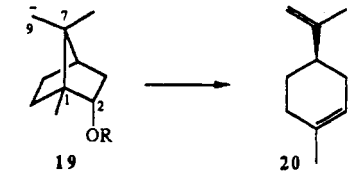
Assignment of an exo or endo orientation of substituents in bicyclo[2.2.1]octanes is easily made by ^{1}H NMR coupling constant analysis. A coupling constant of <1 (normally zero) is commonly observed between the C4 bridgehead hydrogen (H_4) and an endo hydrogen at C3 (H_α), while the H_4–exo-H_α coupling constant is on the order of 4 Hz. The assignment of stereochemistry at the carbinol is less obvious. Stereochemistry of the new C–C bond in aldol adducts is normally assigned on the basis of the H_α–H_β ^{1}H NMR coupling constants or on ^{13}C NMR chemical shifts of the α and β carbons.[18] Both of these criteria are based on the assumption of internally hydrogen-bonded structures **16** and **17**. For example, in an



isomer pair, the larger $J_{\alpha\beta}$ (normally 7–12 Hz) is assigned to the threo isomer **17** due to the anti relationship of H_α to H_β. The smaller $J_{\alpha\beta}$ (normally 0–4 Hz) is assigned to the erythro isomer **16** due to the gauche relationship of H_α to H_β, predicting a relatively small coupling constant. This criterion has been complemented by ^{13}C NMR correlations of Heathcock. For this latter criterion to be reliable, both isomers should be available for comparison. In our cases only one isomer of each erythro–threo pair was obtainable. The exo isomers were assigned the full structure **14** on the basis of the observation of a $J_{\alpha\beta}$ coupling constant of 9–10 Hz in all exo cases except where R = *t*-Bu ($J_{\alpha\beta}$ = 6–7 Hz). This was confirmed by an X-ray crystallographic analysis of the major adduct of benzaldehyde.[19] The endo adducts also displayed $J_{\alpha\beta}$ of 9–10 Hz in all cases except where R = *t*-Bu ($J_{\alpha\beta}$ = 6–7 Hz). Assuming internal hydrogen bonding, this is consistent with the threo structure **15**.

The anionic fragmentation of the C1–C7 bond was made possible by the ready conversion of camphor to 9-bromocamphor in a well-known three-step process. This sequence can routinely be carried out on multihundred gram scales with an overall yield for the three steps on the order of 20–30% when using a slight variation of the procedure of Lawrence,[20] which is reproduced in the Experimental Section for convenience. We reasoned that if negative charge character could be developed at the C9 position while there was a leaving group at the C2 position, a fragmentation might occur, cleaving the desired bridging bond (**19** → **20**). We predicted that an endo leaving group





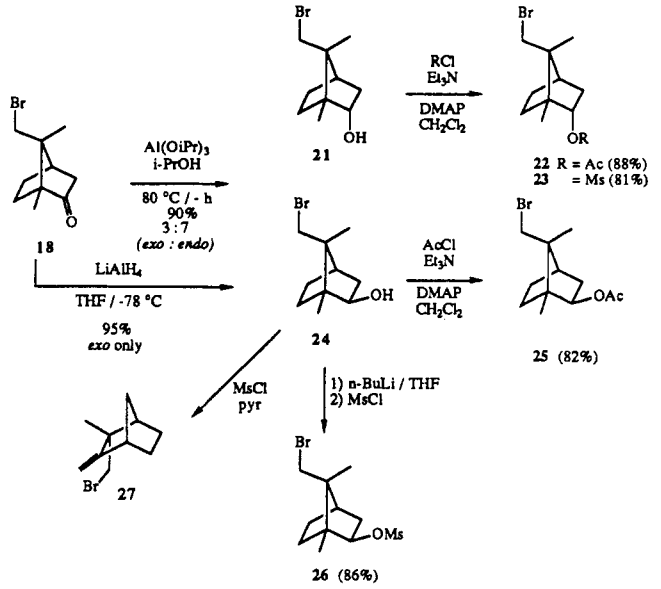
at C2 would participate in a fragmentation more readily than a C2-exo leaving group because of the more favorable overlap of the C2 endo bond with the C1–C7 bond. This is easily seen by inspection of Dreiding models and confirmed by molecular mechanics calculations,[21] which show that the C7–C1–C2-exo dihedral angle is about 91° while the C7–C1–C2-endo dihedral angle is about 165°. We eventually examined both the orientation dependence and leaving group dependence of model fragmentations.

The desired model substrates were synthesized as shown in Scheme II. Meerwein–Verley–Ponndorf reduction was the only method found to generate sufficient quantities of the endo alcohol **21**. Mesylation and acetylation of the endo isomer proceeded without event; however, standard mesylation (MsCl/Et_3N/DMAP) of the exo isomer **24** provided the alkene **27** as the sole product. The exo mesylate apparently could not survive the ionizing conditions at the temperatures required for its formation, instead undergoing cationic rearrangement to **27**. The desired exo mesylate **26** was generated in good yield by deprotonation at low temperature with *n*-BuLi/THF and quenching with MsCl. Fragmentation of the endo mesylate **23** to (+)-limonene (**20**) occurred readily when treated with a solution of sodium naphthalenide (NaNAP) in THF at −78 °C (Scheme III). Limonene was separated only with difficulty from the naphthalene byproduct, accounting for a very low yield. However, ^{1}H NMR of the crude reaction product shows **20** to be the major product of the fragmentation, along with a small amount of the corresponding simple debromination product. A number of other reducing agents were unsuccessful, resulting either in debromination (Li/NH_3, sodium (dimethylamino)naphthalenide[22] (NaDMAN)) or no reaction (*t*-BuLi/THF or Zn/refluxing dioxane).

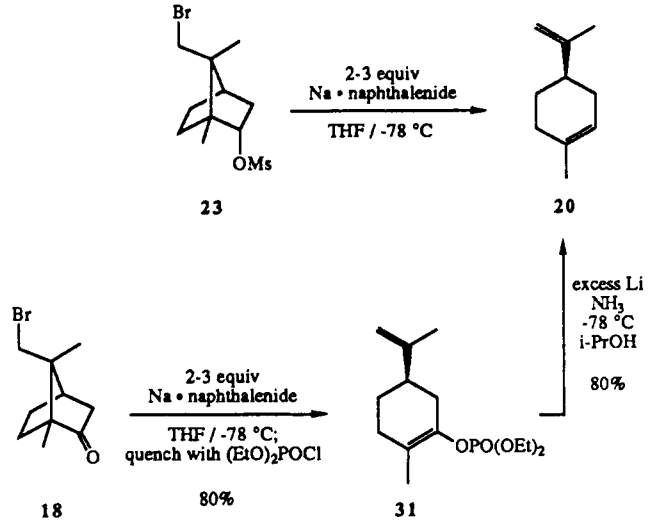
Unfortunately, the exo mesylate **26** behaved as predicted and did not undergo the fragmentation reaction when treated with electron-transfer agents. Instead, simple debromination to **29a** was the major reaction pathway. In

(18) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.
(19) To be reported in a manuscript concerning C2 alkylations and aldol reactions of camphor and related materials. The X-ray structure of **14** (R = Ph) has been previously reported, however. See: Harlow, R. L.; Simonsen, S. H. *Cryst. Struct. Commun.* **1976**, *5*, 471.
(20) David Lawrence, Ph.D. Dissertation, UCLA, 1982.
(21) Calculations were performed on a Macintosh IIx PC using the MM2 force field coupled to the graphics program Chem 3D.
(22) Bank, S.; Platz, M. *Tetrahedron Lett.* **1973**, 2097.

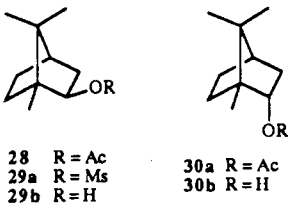
Scheme II. C2 Derivatization of 9-Bromocamphor



Scheme III. Fragmentation of Camphor Derivatives



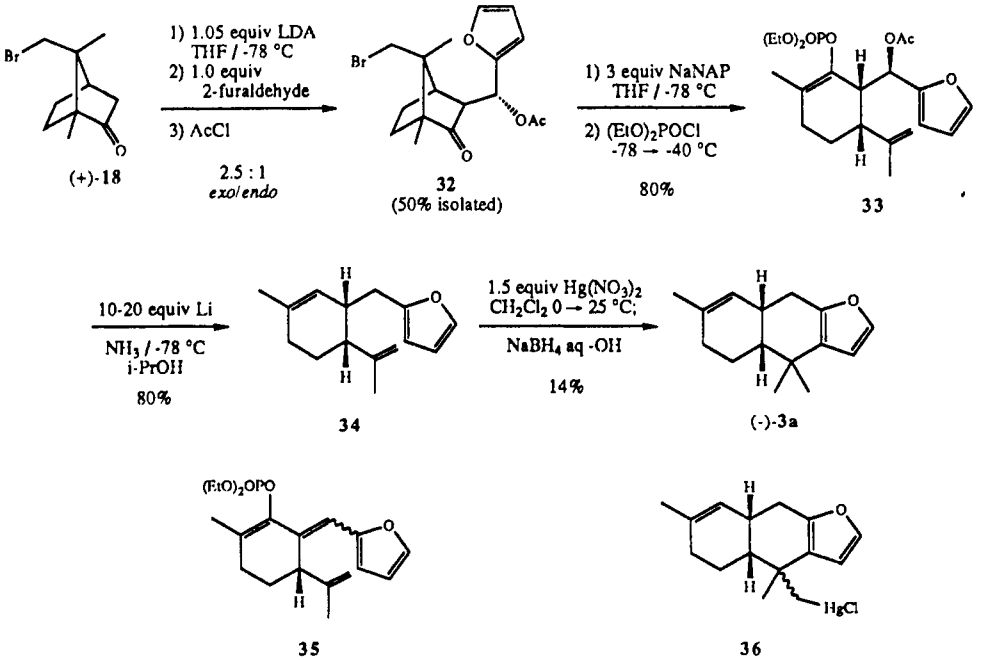
addition to this orientational dependence, we also found that the nature of the leaving group was important. Both the exo and endo acetates **22** and **25** also underwent primarily simple debromination to **28** and **30a,b**, respectively, on treatment with NaNAP or NaDMAN with no fragmentation product detectable by spectroscopic analysis of the crude reaction product.



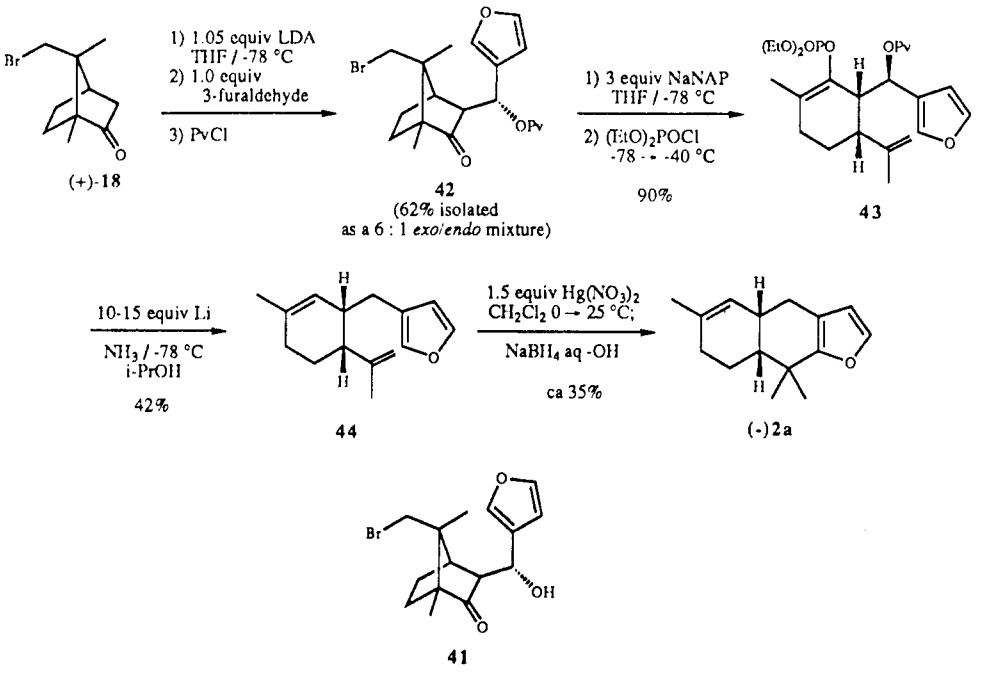
Despite the success of the endo mesylate fragmentation, this was not a completely satisfactory solution, because of the moderate stereoselectivity of the MVP reduction step. Examination of an energy-minimized model of 9-bromocamphor suggests that the dihedral angle between the C1–C7 bond and the carbonyl π-orbitals approximates the C7–C1–C2-endo dihedral angle. Accordingly, γ-bromo ketone fragmentation appeared favorable in this system. On treatment with NaNAP in THF at −78 °C **18** underwent clean fragmentation to an enolate, which could be regiospecifically trapped with diethyl phosphorochloridate to yield the vinyl phosphate **31** in 80% yield as the sole reaction product. Treatment of this substance with excess lithium in NH_3 provided (+)-limonene in 80% yield, thus replacing the carbonyl reduction step with a post-fragmentation phosphate reduction.

With the results of the model studies of the C3 alkylation and fragmentation in hand, we turned our efforts toward the synthesis of **2a** and **3a**. Aldol reaction between 2-furaldehyde and the enolate of **18** yielded a 2.5:1 exo/endo aldol adduct mixture, which could be used without further purification (Scheme IV). The mixture was acylated under standard conditions and a single recrystallization of the acylation products furnished the pure exo acetate **32** in approximately 50% overall yield. It was subsequently found that the adduct mixture from the aldol reaction could be acetylated in situ with acetyl chloride

Scheme IV. Synthesis of (−)-Furodysinin ((−)-3a)



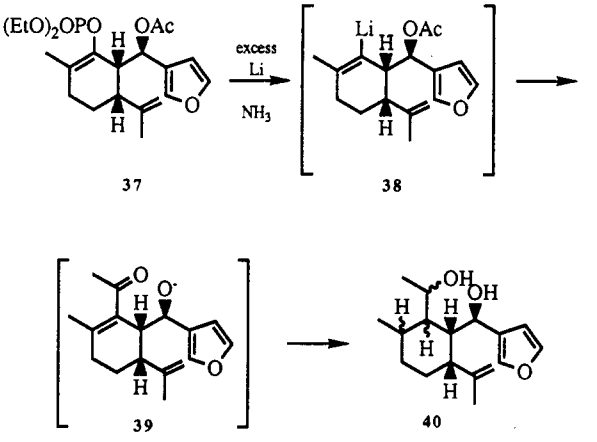
Scheme V. Synthesis of (-)-Furodysin ((-)-2a)



to provide the same exo/endo mixture of acetates. The exo acetate was then treated with 3 equiv of NaNAP in THF at low temperature and the resulting enolate was trapped with diethyl phosphorochloridate, retaining the integrity of the double bond to provide **33**. Care must be taken when preparing the NaNAP reagent since excess sodium caused the reagent to induce elimination of **33** to provide the diene **35** as the major product. The enol phosphate **33** was then subjected to lithium/ammonia reduction, which cleaved not only the phosphate but the acetate as well, resulting in the desired cis-substituted cyclohexene **34**.

A variety of Lewis acids were used in attempts to cyclize **34**. Cyclizations with ZnI_2 yielded only starting material, and the products from cyclization with neat trifluoroacetic acid no longer exhibited furan ring resonances in the ^1H NMR spectra. Although $Tl(OCOCF_3)_3$ appeared to give the desired cyclized products, these did not de-thallate under standard reductive conditions. The best results were obtained by using mercury(II) salts. Cyclization with $Hg(NO_3)_2$ gave 14% of the desired cyclized organomercurial. This could then be demercurated quantitatively to afford furodysinin, which was spectroscopically identical with a sample of (+)-furodysin provided by Dr. Brad Carte. The reduction step was most conveniently carried out in situ and the resulting (-)-**3a** exhibited $[\alpha]_D$ -54°, thus allowing assignment of the first absolute configuration in this series. The overall pathway consists of four operations from 9-bromocamphor.

The versatility of this approach is illustrated by the simple variation required to produce the isomeric metabolite series in the form of furodysin (Scheme V). The aldol reaction of 3-furaldehyde with **18** gave rise to a 4:1 mixture of exo/endo adducts. Although the acetylation and fragmentation steps proceeded smoothly, dissolving metal reduction of **37** gave rise to the desired **43** in ca. 10% yield along with a variety of products, the major of which is **40**. The structure of **40** was assigned on the basis of its combined spectroscopic data. This substance is stereochemically homogeneous but the relative stereochemistry at the designated centers remains unassigned. A reasonable pathway for the formation of **40** is via intramolecular acyl transfer within the intermediate vinyl anion **38**, providing enone **39**, which undergoes complete reduction of the enone system under the conditions of excess Li. After unsuccessful attempts at varying the reduction conditions to change the product ratios, the aldol adduct **41** was then derivatized in various ways. Although conversion of the hydroxyl to nontransferable ether derivatives seemed like the obvious solution, attempts to convert the hydroxyl of **41** to a silyl or MOM ether were accomplished only in low yield. Reasoning that a more hindered ester would undergo acyl transfer more slowly, the pivalate ester was readily formed by trapping the aldol adduct mixture with pivaloyl chloride providing a 6:1 exo/endo mixture of pivalates in 62% yield after recrystallization. Fragmentation of the C1–C7 bond of this mixture by reduction with sodium naphthalenide occured in 90% yield (based on the exo isomer) to provide **43**. Reduction of this substance with Li/NH_3 as before provided a much improved 42% yield of the desired cyclization precursor **44**. Treatment of **44** under the same cyclization conditions as **34** led to a much cleaner reaction mixture, giving furodysin in 35% yield after chromatography on silica. The substance was spectroscopically identical with natural (+)-furodysin. The $[\alpha]_D$ value was measured to be -36°,[23] thus establishing



absolute configurations in the dysin metabolite series. By this route, optically active (−)-furodysin can be synthesized in four steps in approximately 7% overall yield from **18**.

Summary

Syntheses of both (−)-furodysinin ((−)-**3a**) and (−)-furodysin ((−)-**2a**) using analogous pathways have been accomplished from (+)-9-bromocamphor in four steps, establishing the absolute configurations in both the dysin and dysinin metabolite series. This was facilitated by the unexpected exo stereoselectivity in the aldol reaction of camphor enolates with aldehydes, which was shown to be a general phenomenon. Additionally, new fragmentation reactions of the camphor system were uncovered, allowing camphor derivatives to be used as six-membered ring chiral pool elements. Adaptations of this and related technology to the synthesis of the more highly oxidized and more biologically active furanosesquiterpenes in this category are currently under way.

Experimental Section

General. ^1H NMR data were measured at 300 MHz and ^{13}C data at 75 MHz. NMR spectral data taken in $CDCl_3$ used the residual $CHCl_3$ singlet at δ 7.26 as the standard for ^1H data and the triplet centered at δ 77.0 as the standard for ^{13}C spectra. Data taken in C_6D_6 used the singlet for residual C_6D_5H at δ 7.16 as the ^1H standard and the triplet at δ 128.0 for the ^{13}C standard. Infrared spectroscopic samples were prepared as neat oils (liquids) or as KBr pellets (solids). All electron impact high resolution mass spectral (HRMS) data were measured at 70 eV. Optical rotations were measured at the designated concentrations at 25 °C on a Perkin-Elmer Model 241MC polarimeter. All of the experiments were carried out under an atmosphere of dry nitrogen in flame-dried flasks fitted with addition funnels of the pressure equilibrating type. THF and diethyl ether were freshly distilled from sodium/benzophenone ketyl and were transferred via syringes. Diisopropylamine and hexamethyldisilazane were distilled from CaH_2 under nitrogen. Alkyllithium reagents were obtained from the Aldrich Chemical Company as standardized solutions. Mercury(II) nitrate was dried in a drying pistol under vacuum with refluxing toluene. High performance liquid chromatography (HPLC) was performed on either a Varian 5000 liquid chromatograph or a semipreparative component system obtained from the Rainin Instrument Corporation. HPLC separations were performed on 250 × 20 mm 8μ silica Magnum semi-preparative columns obtained from Rainin. In vacuo removal of solvent refers to the use of a rotary evaporator operating at aspirator pressure.

Synthesis of (+)-9-Bromocamphor (18). (+)-*endo*-3-Bromocamphor. A 5-L three-necked round-bottom flask fitted with a thermometer, addition funnel, and a condensor, which led to a bubbler, was charged with 1000 g (6.56 mol) of (+)-camphor and 2.5 L of HOAc. The solution was heated to 80–90 °C and a solution of 400 mL of bromine (1240 g, 7.75 mol) in 400 mL of HOAc was added slowly such that the deep red color of bromine was not allowed to build up (about 8 h). The reaction was stirred at about 80 °C for 6 h after the addition had ended. The reaction was then cooled to room temperature and transferred in portions to an addition funnel. The reaction mixture was allowed to drip into about 6 L of ice water with stirring. A white granular precipitate resulted. This was filtered off and washed with 1-L portions of water until the filtrate was colorless. The solid was sucked dry on a Buchner funnel and air dried for a day. The crude reaction product is only about 5% impure, but it can be recrystallized from 1 L of 95% EtOH to give 1055 g (69%) of white crystals spectroscopically identical with commercial material. This substance was used in the next reaction.

(+)-*endo*-3,9-Dibromocamphor. A 2-L three-necked flask fitted with a thermometer, a stopper, and a condensor that led to a bubbler was charged with 400 mL of chlorosulfuric acid. The liquid was cooled to 10 °C and 118.5 mL (367.5 g, 2.30 mol) of bromine was added carefully with stirring. While cooling with an ice bath, 500 g (2.16 mol) of (+)-*endo*-3-bromocamphor was added as a solid in portions such that the temperature did not rise above about 25 °C. During the addition HBr was given off vigorously. The HBr evolution ceased after the addition had been over for 2 h and the reaction was allowed to stir for an additional 5 h. The reaction mixture was poured into an addition funnel and added slowly to ice water (about 3 L) with stirring or shaking. A white solid precipitated immediately. A few grams of solid $NaHSO_3$ was added and the mixture was stirred for 30 min. The white solid was filtered off and washed successively with four 1-L portions of water. The slightly yellow solid was sucked as dry as possible on a Buchner funnel. The crude product was recrystallized from 1500 mL of hot ethanol to leave 427 g (63%) of white crystals, which were spectroscopically identical with commercially available material.[24] $[\alpha]_D$ = +95.5° (c = 4.26, $CHCl_3$).

(+)-9-Bromocamphor (18). Into a 5-L Erlenmeyer flask was placed 400 g of (+)-*endo*-3,9-dibromocamphor (1.29 mol) partially dissolved in 2400 mL of HOAc. The mixture was cooled to approximately 15 °C with an ice bath, and Zn dust (261 g, 4.0 mol) was added in small portions such that the temperature did not rise above about 25 °C. There was a small induction period before reaction occurred after each addition. The reaction was stirred for 2 h after the end of the addition. The reaction mixture was filtered through fluted filter paper into a separatory funnel and diluted with ether. The ether was washed with water 3–5 times followed by washing with aqueous saturated $NaHCO_3$ solution (4–5 times) until gas evolution ceased. The ether layer was dried (Na_2SO_4) and the solvent removed in vacuo. The crude reaction product was recrystallized twice from hexane (with cooling to −20 °C overnight) to provide 179.0 g (60%) of white crystals: $[\alpha]_D$ = +115° (c = 1.26, $CHCl_3$).

***exo*-9-Bromobornan-2-ol (24).** A 250-mL flame-dried three-necked flask equipped with a condensor and an addition funnel was charged with 1.23 g (32.4 mmol) of $LiAlH_4$ and 40 mL of dry THF and cooled to −78 °C. To this was added dropwise a solution of 10.0 g (43.3 mmol) of (+)-9-bromocamphor (**18**) in 40 mL of dry THF. The mixture was stirred at −78 °C for an additional hour. The reaction was quenched with 2.5 mL of H_2O, 2.5 mL of 15% aqueous NaOH, and 7.5 mL of H_2O. The crude reaction product was diluted with ether, filtered, dried over Na_2SO_4, and concentrated to give a white solid. Recrystallization from hexane yielded 9.42 g (93%) of pure *exo*-9-bromobornan-2-ol (**24**): mp 105–107 °C; $[\alpha]_D$ = −3.1° (c = 3.91 × 10^{-3}, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.72 (t, 1 H, J = 5.6, 5.7 Hz), 3.53 (dd, 1 H, J = 1, 10 Hz), 3.20 (d, 1 H, J = 10 Hz), 2.11 (d, 1 H, J = 2 Hz), 1.7–1.55 (overlapping m, 5 H), 1.15 (bm, 2 H), 1.25 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 80.6, 76.6, 50.8, 43.1, 41.9, 39.1, 33.2, 26.0, 15.7, 11.2; IR (KBr) 3347, 1450, 1239, 907 cm^{-1}; high resolution MS m/z calcd for $C_{10}H_{16}Br$ (M^+ − OH) 215.0435, obsd 215.0439.

***endo*-9-Bromobornan-2-ol (21).** A 250-mL three-necked flask equipped with a condensor was charged with 10.0 g (43.3 mmol) of (+) 9-bromocamphor (**18**), 22.0 g (107.5 mmol) of aluminum isopropoxide, and 150 mL of dry 2-propanol. The reaction mixture was heated to 90 °C and stirred for 4 days, at which time it was quenched with 50 mL of saturated $NaHCO_3$. The mixture was filtered and the filtrate was extracted three times with ether. The organic extracts were combined, dried over Na_2SO_4, and concentrated to give 9.29 g (92%) of a 6.5:3 mixture of *endo*/*exo*-9-bromobornan-2-ols. Medium pressure liquid chromatography using 80:20 hexane/ethyl acetate as eluant gave 5.56 g (55% yield) of *endo*-9-bromobornan-2-ol (**21**) and 2.55 g (25% yield) of *exo*-9-bromobornan-2-ol (**24**). Data for **21**: mp 126–127 °C; $[\alpha]_D$ = +3.7° (c = 3.21 × 10^{-3}, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.00 (d, 1 H, J = 9.3 Hz), 3.60 (dd, 1 H, J = 1, 10.5 Hz), 3.20 (d, 1 H, J = 10.5 Hz), 2.20 (m, 1 H), 2.00 (m, 3 H), 1.70 (m, 1 H), 1.30 (m, 2 H), 1.01 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 77.5, 52.1, 50.6, 43.2, 41.5, 37.8, 27.529, 25.6, 14.9, 13.4; IR (KBr) 3398, 1452, 1242, 949, 663 cm^{-1}; high resolution MS m/z calcd for $C_{10}H_{15}Br$ (M^+ − H_2O) 214.0357, found 214.0361.

(23) The $[\alpha]_D$ value reported by Wells (ref 3) for the (+) enantiomer is +36° (c = 0.5, $CHCl_3$).

(24) Obtained from the Aldrich Chemical Company.

***endo*-9-Bromobornan-2-ol Acetate (22).** A solution of 1.0 g (4.29 mmol) of *endo*-9-bromobornan-2-ol (**21**) dissolved in 20 mL of CH_2Cl_2 was stirred in a 125-mL Erlenmeyer flask. To this were added 3.00 mL (21.52 mmol) of triethylamine and 26.1 mg (0.214 mmol) of 4-(dimethylamino)pyridine, and the mixture was cooled to −10 °C. Acetyl chloride (1.83 mL, 25.7 mmol) was then added dropwise. The reaction mixture was warmed to room temperature and stirred for several hours. The reaction was quenched with 20 mL of 6% aqueous HCl and extracted once with 20 mL of CH_2Cl_2. The combined organic extracts were washed twice with 20-mL portions of 6% HCl, three times with 20-mL portions of saturated $NaHCO_3$ solution, twice with 20-mL portions of saturated NaCl solution, dried over Na_2SO_4, and evaporated to give 1.04 g (88%) of the acetate **22** as a pale yellow solid. Recrystallization from methanol yielded colorless endo acetate: mp 51–53 °C; $[\alpha]_D = +29.9°$ ($c = 3.08 \times 10^{-3}$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.90 (qd, 1 H, J = 5.7, 13.5), 3.60 (dd, 1 H, J = 0.9, 9.3 Hz), 3.18 (d, 1 H, J = 10.2 Hz), 2.26 (m, 1 H), 2.10 (m, 3 H), 2.06 (s, 3 H), 1.75 (m, 1 H), 1.40 (m, 2 H), 1.09 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 79.8, 52.1, 49.9, 43.2, 40.8, 35.9, 27.4, 26.9, 21.3, 15.2, 13.7; IR (KBr) 2956, 1739, 1457, 1243, 669 cm^{-1}; high resolution MS m/z calcd for $C_{10}H_{16}Br$ (M^+ − OAc) 215.0435, found 215.0441.

***exo*-9-Bromobornan-2-ol Acetate (25).** The same procedure used to prepare **22** was utilized to prepare **25** from **24** and 0.97 g (82%) of the exo acetate **25** was obtained as a pale yellow oil from 1.0 g (4.29 mmol) of **24**: $[\alpha]_D = -23.6°$ ($c = 4.71 \times 10^{-3}$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.70 (dd, 1 H, J = 3.6, 7.8 Hz), 3.46 (dd, 1 H, J = 0.9, 10 Hz), 3.17 (d, 1 H, J = 10.2 Hz), 2.05 (t, 1 H, J = 7.5 Hz), 1.99 (s, 3 H), 1.85–1.55 (m, 5 H), 1.13 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.4, 81.8, 51.8, 50.0, 43.6, 41.6, 37.9, 33.6, 26.3, 21.3, 16.1, 11.8; IR (KBr) 2978, 1736, 1448, 1243, 1055, 674 cm^{-1}; high resolution MS m/z calcd for $C_{12}H_{19}O_2$ (M^+ − Br) 195.1384, found 195.1381.

***endo*-9-Bromobornan-2-ol Mesylate (23).** A solution of 1.0 g (4.29 mmol) of *endo*-9-bromobornan-2-ol (**21**) dissolved in 20 mL of CH_2Cl_2 was placed in a 125-mL Erlenmeyer flask. To this were added 3.00 mL (21.5 mmol) of triethylamine and 26.1 mg (0.21 mmol) of 4-(dimethylamino)pyridine, and the mixture was cooled to −10 °C. Methanesulfonyl chloride (2.00 mL, 25.7 mmol) was then added dropwise. The reaction mixture was warmed to room temperature and stirred for several hours. The reaction was quenched with 20 mL of 6% aqueous HCl and extracted once with 20 mL of CH_2Cl_2. The combined organic extracts were washed twice with 20-mL portions of 6% HCl, three times with 20-mL portions of saturated $NaHCO_3$, and twice with 20-mL portions of saturated NaCl, dried over Na_2SO_4, and evaporated to give 1.09 g (81%) of the endo mesylate **23** as a white solid. Recrystallization from methanol gave colorless **23**: $[\alpha]_D = +10.4°$ ($c = 3.86 \times 10^{-3}$, $CHCl_3$); mp 95–96 °C; ^1H NMR ($CDCl_3$) δ 4.80 (m, 1 H), 3.57 (dd, 1 H, J = 1.2, 10.5 Hz), 3.17 (d, 1 H, 10.5 Hz), 2.99 (s, 3 H), 2.35 (m, 1 H), 2.10 (m, 1 H), 2.01 (m, 1 H), 1.77 (m, 1 H), 1.40 (m, 3 H), 1.07 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 86.9, 43.2, 39.8, 38.2, 35.6, 27.2, 26.4, 15.1, 13.2; IR (KBr) 3026, 1457, 1347, 1244, 1177, 876 cm^{-1}; high resolution MS m/z calcd for $C_{11}H_{19}O_3S$ (M^+ − Br) 231.1055, found 231.1060.

***exo*-9-Bromobornan-2-ol Mesylate (26).** A three-necked 100-mL round-bottom flask was charged with 1.0 g (4.29 mmol) of *exo*-9-bromobornan-2-ol (**24**) and 10 mL of dry THF. To this were added dropwise a solution of 1.89 mL (4.72 mmol) of a 2.5 M solution of *n*-butyllithium, and the reaction mixture was held at −78 °C for 30 min. Then 0.5 mL (6.45 mmol) of methanesulfonyl chloride was added dropwise and the reaction mixture stirred for an additional 20 min at −78 °C, warmed to −20 °C, and quenched with 20 mL of saturated $NaHCO_3$ solution. The reaction mixture was worked up very quickly with three 20-mL portions of ether and the combined organic extracts were washed twice with 20-mL portions of water and once with a 20-mL portion of saturated NaCl, dried in an ice bath over Na_2SO_4, and evaporated to give 1.15 g (86%) of the exo mesylate **26** as white crystals. The mesylate can be stored for several months at −20 °C: mp 23–24 °C; $[\alpha]_D = -25.6°$ ($c = 2.62 \times 10^{-3}$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.60 (dd, 1 H, J = 3.3, 7.8 Hz), 3.47 (dd, 1 H, J = 1.2, 10.2 Hz), 3.20 (d, 1 H, J = 10.2 Hz), 2.98 (s, 3 H), 2.12 (m, 1 H), 1.92 (dd, 2 H, J = 7.8, 13.8 Hz), 1.70 (m, 3 H), 1.17 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 89.4, 52.0, 43.8, 40.7, 38.5, 38.5, 33.5, 26.1, 16.1, 12.1; IR (KBr) 3019, 1455, 1345, 1171, 745, 636 cm^{-1}; high resolution MS m/z calcd for $C_{10}H_{15}Br$ (M^+ − OSO_2Me) 214.0357, found 214.0363.

Preparation of 0.4 M Sodium 1-(Dimethylamino)-naphthalenide (NaDMAN). A single-necked 250-mL round-bottom flask was charged with 100 mL of dry THF and 6.57 mL (40 mmols) of 1-(dimethylamino)naphthalene. To this was added 1.0 g (43.5 mmols) of freshly cut sodium metal, and the reaction mixture was stirred at room temperature for 2–3 h before use.

Fragmentation of *endo*-9-Bromobornan-2-ol Acetate (22) with NaDMAN. A three-necked flask was charged with 0.35 g (1.27 mmol) of **22** and 10 mL of dry THF and cooled to −78 °C. To this was added dropwise 7 mL (2.8 mmol) of NaDMAN solution prepared as stated above until a dark green color persisted. The reaction mixture was allowed to stir for an additional 15 min, warmed to −20 °C, and quenched with 20 mL of a saturated NH_4Cl solution. The mixture was extracted three times with 20-mL portions of ether and the combined extracts were washed three times with 20-mL portions of 6% HCl, twice with 20-mL portions of saturated $NaHCO_3$, and once with 20-mL portions of saturated NaCl, dried over Na_2SO_4, and evaporated to give a yellow liquid. Purification by flash chromatography using 80% hexane/20% ethyl acetate as eluant gave 0.139 g (55%) of bornyl acetate (**30a**) an 0.049 g (25%) of borneol (**30b**) as colorless solids. The structures of the products were confirmed by spectral comparison with samples prepared by acetylation of borneol.

Fragmentation of *exo*-9-Bromobornan-2-ol Acetate (25) with NaDMAN. The procedure used for fragmentation of **22** was employed with 0.35 g (1.27 mmol) of **25** and 7.0 mL (2.8 mmol) of NaDMAN solution (prepared as stated above) to give 0.187 g (75%) of isobornyl acetate (**28**) after recrystallization from hexane. The structure of the product was confirmed by spectral comparison with samples prepared by acetylation of isoborneol.

Fragmentation of *exo*-9-Bromobornan-2-ol Mesylate (26) with NaDMAN. A three-necked flask was charged with 0.35 g (1.12 mmol) of **26** and 10 mL of dry THF and cooled to −78 °C. To this was added dropwise 13.9 mL (5.56 mmol) of NaDMAN solution (prepared as described above) until a dark green color persisted. The reaction mixture was allowed to stir for an additional 15 min, warmed to −20 °C, and quenched with 20 mL of a saturated NH_4Cl solution. The mixture was extracted quickly three times with 20-mL portions of ether, and the combined extracts were washed with three 20-mL portions of cold 6% HCl, two 20-mL portions of cold saturated $NaHCO_3$, and one 20-mL portion of saturated NaCl, dried over Na_2SO_4, and evaporated to give a yellow liquid. Recrystallization from hexane gave 0.222 g (85%) of isobornyl mesylate as a white solid, spectroscopically identical with material prepared by mesylation of isoborneol.

Fragmentation of *endo*-9-Bromobornan-2-ol Mesylate (23) with NaDMAN. A three-necked flask was charged with 0.35 g (1.12 mmol) of **23** and 10 mL of dry THF and cooled to −78 °C. To this was added dropwise 13.9 mL (5.56 mmol) of NaDMAN solution (prepared as stated above) until a dark green color persisted. The reaction mixture was allowed to stir for an additional 15 min, warmed to −20 °C, and quenched with 20 mL of a saturated NH_4Cl solution. The mixture was extracted three times with 20-mL portions of ether and the combined extracts were washed three times with 20-mL portions of 6% HCl, twice with 20-mL portions of saturated $NaHCO_3$, and once with 20 mL of saturated NaCl, dried over Na_2SO_4, and evaporated to give a yellow liquid. Recrystallization from hexane gave 0.193 g (74%) of bornyl mesylate as the major product.

Fragmentation of *endo*-9-Bromobornan-2-ol Mesylate (23) with 0.4 M Sodium Naphthalenide/0.4 M Tetraethylene Glycol Dimethyl Ether. A 100-mL three-necked flask was charged with 0.35 g (1.12 mmol) of **23** and 10 mnL of dry THF and cooled to −78 °C. To this was added 18 mL (7.2 mmol) of sodium naphthalenide solution (prepared as stated below) until a dark green color persisted. The reaction mixture was allowed to stir for an additional 15 min, warmed to −20 °C, and quenched with 20 mL of a saturated NH_4Cl solution. The mixture was extracted three times with 20-mL portions of ether, twice with 20-mL portions of water, and once with a 20-mL portion of saturated NaCl, dried over Na_2SO_4, and evaporated to give a mixture of naphthalene and limonene. Purification by crystallization from hexane removed the bulk of the naphthalene, leaving

behind the limonene in the mother liquor. High performance liquid chromatography of this residue using hexanes as eluant gave (+)-limonene (**20**) as a clear oil. This substance was spectroscopically identical with commercial material and displayed $[\alpha]_D = +118.6°$ ($c = 2.8 \times 10^{-3}$, $CHCl_3$).

General Procedure for the Aldol Reaction of Camphor with Aldehydes. Lithium diisopropylamide (LDA) was prepared by reaction of diisopropylamine (1.00 mL, 7.0 mmol) with *n*-butyllithium (2.50 mL of a 2.5 M solution in hexanes, 6.25 mmol) in 4 mL of dry THF at −78 °C. The solution was stirred for 15 min and a solution of camphor (0.91 g, 6.0 mmol) in 4 mL of dry THF was added dropwise (time of addition 15 min). After the addition, the solution was stirred for 1.5 h and treated with 6.0 mmol of freshly distilled aldehyde and stirred for an additional 15 min. The reaction was quenched at −78 °C with a saturated aqueous solution of $NaHCO_3$ (50 mL). The cold bath was then removed and the mixture extracted three times with 50-mL portions of ether. The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to afford the adduct mixture. Data on the individual exo and endo adducts will be found in a subsequent manuscript currently in preparation dealing with the alkylation and aldol reaction chemistry of bicyclo[2.2.1]heptan-2-ones and related substances.

Fragmentation of (+)-9-Bromocamphor (18) to 31. (+)-9-Bromocamphor (**18**) (0.100 g, 0.43 mmol) was submitted to the general fragmentation conditions (using NaNAP) and was followed by trapping with 1–2 equiv of diethyl phosphochloridate. Workup as in the preparation of **42** (below) followed by chromatography on silica led to 0.099 g (80% yield) of **31**: $[\alpha]_D = +49°$ ($c = 7.3 \times 10^{-3}$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.69 (s, 2 H), 4.16–4.07 (m, 4 H), 2.35–2.17 (bm, 3 H), 2.10–1.90 (bm, 2 H), 1.69 (s, 3 H), 1.64 (s, 3 H), 1.50–1.34 (om, 2 H), 1.33–1.28 (t, 6 H); ^{13}C NMR ($CDCl_3$) δ 148.2, 140.2, 118.0, 109.1, 63.7, 41.9, 32.9, 30.0, 27.1, 20.5, 15.9; IR (neat) 3084, 2984, 2932, 2861, 1705, 1646, 1443, 1271, 1142, 1034, 961; high resolution MS *m/z* calcd 288.1492 (M^+), obsd 288.1490.

Reduction of 31 to (+)-Limonene (20). A solution of 0.5 g (1.8 mmol) of **31** in 10 mL of anhydrous THF was added dropwise to a cold (−78 °C) magnetically stirred solution of lithium (30 mg, 4.0 mmol) in liquid ammonia. The reaction was stirred for 0.5 h and then allowed to warm to refluxing temperature until the NH_3 had evaporated. The solution was quenched with 20% aqueous NH_4Cl and extracted with ether (two 20-mL portions), washed with water (two 20-mL portions), dried over Na_2SO_4, and concentrated to give 0.19 g (80%) of limonene (**20**) spectroscopically identical with commercial material.

Pivalate Ester 42. In a 500-mL three-necked flask, lithium diisopropyl amide was generated by treating 10.5 mL (78.5 mmol, 1.1 equiv) of diisopropylamine in 75 mL of dry THF at −78 °C with 30 mL (75 mmol, 1.05 equiv) of *n*-BuLi (2.5 M in hexanes) and stirring for 30 min. To this was added dropwise a solution of 16.5 g (71.5 mmol, 1.0 equiv) of 9-bromocamphor (**18**) in 75 mL of dry THF. The mixture was allowed to stir for 1.5 h at −78 °C and then 6.2 mL (71.5 mmol, 1.0 equiv) of 3-furaldehyde was syringed in dropwise and stirred an additional 15 min. The reaction was then quenched by the addition of 15 mL of HMPA followed by trapping with 22.0 mL (179 mmol, 2.5 equiv) of pivaloyl chloride and allowing the solution to warm to −20 °C. The reaction mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with Et_2O. The combined organic layers were then washed twice with 200-mL portions of saturated aqueous $NaHCO_3$ and twice with 200-mL portions of saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo yielded 34.71 g of a pumpkin-colored solid that was recrystallized twice from 2-propanol to afford 18.37 g (44.7 mmol, 62%) of a 6:1 (exo/endo) mixture of pivalates as pale orange crystals. This mixture could be directly used in the next reaction in the sequence. Physical data on the pure exo pivalate **42** were obtained on an analytically pure sample, using chromatography on silica: $[\alpha]_D = +136.1°$ ($c = 3.00$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.16 (s, 3 H), 1.20 (s, 9 H), 1.41 (m, 1 H), 1.61 (om, 2 H), 1.89 (m, 1 H), 2.14 (s, 1 H), 2.43 (d, $J = 11$, 1 H), 3.13 (d, $J = 10$, 1 H), 3.45 (d, $J = 10$, 1 H), 5.97 (d, $J = 11$, 1 H), 6.36 (d, $J = 1$, 1 H), 7.39 (d, $J = 2$, 1 H), 7.42 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.6, 18.7, 27.0, 28.3, 29.1, 38.5, 40.2, 44.4, 50.3, 56.5, 59.0, 67.6, 108.4, 124.1, 140.5, 143.7, 177.2, 214.0; IR (KBr pellet) 3143, 3123, 3103, 2991, 2971, 2938, 2884, 1756, 1727, 1609, 1138, 1018 cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{27}O_4Br$ (M^+) 410.1093, found 410.1089.

Preparation of 0.4 M Sodium Naphthalenide/0.4 M Tetraethylene Glycol Dimethyl Ether Solution. A 250-mL flask under nitrogen was charged with 11.25 g (87.5 mmol) of naphthalene and 200 mL of dry THF. To this was added 1.85 g (80 mmol) of sodium metal. The mixture was allowed to stir for 1 h and 17.75 mL (80 mmol) of tetraethylene glycol dimethyl ether was added. The mixture was allowed to stir for an additional hour. Excess reagent was stored in a freezer at −25 °C.

Fragmentation of 42. A 250-mL three-necked flask was charged with a solution of 4.1 g (10 mmol) of the exo pivalate in 100 mL of dry THF and cooled to −78 °C. The cold solution was titrated with ca. 80 mL (32 mmol, 3.2 equiv) of the 0.4 M Na-NAP/0.4 M TGDE solution. When a deep green color persisted, 3 mL (17.2 mmol, 1.7 equiv) of HMPA and 2.1 mL of diethyl phosphochloridate (14.5 mol, 1.45 equiv) were syringed in dropwise. The reaction was allowed to warm to −40 °C and quenched by the addition of 100 mL of saturated aqueous NH_4Cl. The solution was transferred to a 500-mL separatory funnel. The aqueous layer was extracted three times with 50-mL portions of Et_2O. The combined organic layers were washed three times with water and twice with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded a pale yellow solid containing the desired product and naphthalene. Flash colum chromatography eluting first with 95:5 hexane/ethyl acetate and then with 70:30 hexane/ethyl acetate yielded 4.22 g (90%) of the desired enol phosphate **43**: $[\alpha]_D = +119°$ ($c = 0.608$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (s, 9 H), 1.18–1.40 (om, 7 H), 1.61 (s, 3 H), 1.72 (s, 3 H), 2.02 (m, 1 H), 2.11 (m, 1 H), 2.37 (m, 2 H), 3.25 (s, 1 H), 4.08 (m, 4 H), 4.82 (s, 1 H), 4.93 (s, 1 H), 5.76 (d, $J = 3$, 1 H), 6.42 (d, $J = 1$, 1 H), 7.29 (d, $J = 4$, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.0, 16.1, 16.5, 22.6, 26.8, 30.0, 38.6, 43.7, 44.6, 63.7, 65.6, 109.5, 112.1, 121.6, 126.8, 139.9, 140.1, 142.5, 145.5, 176.8; IR (cm^{-1}, neat) 3130, 3076, 2984, 2931, 2911, 1735, 1649, 1271, 1158, 1032, 959; HRMS *m/z* calcd for $M^+ - OOCC(CH_3)_3$ 367.16745, found 367.1679.

Reduction of 43 to 44. A 250-mL three-necked flask equipped with a dry ice condenser and an addition funnel was charged with a solution of lithium in NH_3 (ca. 0.75 g, 10 equiv of Li/150 mL of NH_3) at −78 °C. To this was added dropwise a solution of 5 g (10.7 mmol) of the enol phosphate in 1.80 mL (23.5 mmol, 2.2 equiv) of 2-propanol and 25 mL dry THF. The reaction was stirred for 2 h, adding additional lithium when necessary to maintain the deep blue color of the solution. The reaction was allowed to warm slowly to room temperature and quenched (when gas evolution had ceased) by the addition of 30 mL of saturated NH_4Cl. The solution was transferred to a 250-mL separatory funnel. The aqueous layer was extracted three times with 50-mL portions of Et_2O. The combined organic layers were washed twice with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 2.37 g of a pale yellow oil. Flash chromatography eluting with hexanes yielded 0.985 g (4.55 mmol, 43%) of the desired limonene derivative **44**: $[\alpha]_D = +309°$ ($c = 0.728$, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.35 (t, $J = 1$, 1 H), 7.18 (s, 1 H), 6.26 (d, $J = 1$, 1 H), 5.41 (m, 1 H), 4.90 (s, 1 H), 4.73 (s, 1 H), 2.41 (br s, 1 H), 2.37 (d, $J = 4$, 1 H), 2.25 (m, 1 H), 2.12 (br s, 1 H), 2.08 (d, $J = 3$, 1 H), 2.02 (br t, $J = 3$, 1 H), 1.79 (s, 3 H), 1.67 (overlapping m, 2 H), 1.65 (s, 3 H); ^{13}C NMR δ 22.5, 22.8, 23.5, 25.9, 30.7, 36.7, 43.8, 110.1, 111.5, 123.8, 125.0, 133.8, 139.4, 142.5, 147.6; IR (cm^{-1}, neat) 3083, 3024, 2984, 2924, 2884, 1649, 1497, 1443, 1028, 899, 872; HRMS *m/z* calcd for $C_{15}H_{20}O$ 216.1514, found 216.1517.

(−)-Furodysin ((−)-2a). A 50-mL flask was charged with 0.170 g (0.79 mmol) of the limonene derivative and 20 mL of dry CH_2Cl_2. The mixture was cooled to 0 °C and 0.383 g (1.18 mmol, 1.5 equiv) of anhydrous $Hg(NO_3)_2$ was added. The mixture was allowed to warm slowly to room temperature and stirred for an additional 2 h. The mixture was then cooled back to 0 °C and 1.74 mL (ca. 7.9 mmol, 10 equiv) of a 12% wt solution of $NaBH_4$ in 14 N NaOH was added. The resulting solution was allowed to warm slowly to room temperature and stirred for an additional 2 h. The mixture was then filtered through Florisil and diluted with water. The layers were separated and the aqueous layer was extracted

three times with Et_2O. The combined organic layers were washed three times with 50-mL portions of saturated aqueous $NaHCO_3$ and three times with 50-mL portions of saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo afforded 0.181 g of a bright yellow oil. Flash chromatography eluting with hexanes yielded 0.061 g (35%) of synthetic (−)-**2a** as long colorless spears, which were spectroscopically identical with natural furodysin: mp 71–73 °C (lit.[3] mp 75 °C; $[\alpha]_D$ = −38° (c = 0.096, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.27 (s, 3 H), 1.35 (m, 2 H), 1.60 (overlapping m, 1 H), 1.66 (s, 3 H), 1.75 (m, 1 H), 2.06 (m, 1 H), 2.19 (m, 1 H), 2.56 (overlapping m, 2 H), 5.60 (m, 1 H), 6.10 (d, J = 2, 1 H), 7.23 (d, J = 2, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.5, 23.2, 23.8, 27.3, 30.7, 31.6, 31.7, 34.5, 45.6, 109.8, 112.9, 126.4, 133.1, 140.4, 156.8; IR (cm^{-1}, KBr pellet) 3143, 3110, 3017, 2957, 2924, 1676, 1636, 1576, 1503, 1457, 1384, 1144, 739, 726; high resolution MS m/z (M^+) calcd for $C_{15}H_{20}O$ 216.1514, found 216.1518.

Aldol Reaction of (+)-9-Bromocamphor with 2-Furaldehyde. In a 250-mL three-necked flask, LDA was generated by treating 11.0 mL (78.75 mmol, 1.10 equiv) of diisopropylamine with 30 mL (75 mmol, 1.05 equiv) of n-BuLi (2.5 M in hexanes) at −78 °C and stirring the solution for 30 min. To this was added dropwise a solution of 16.5 g (71.5 mmol, 1.0 equiv) of **18** in 75 mL of dry THF. The mixture was allowed to stir for 1.5 h at −78 °C and then 5.92 mL (71.5 mmol, 1.0 equiv) of 2-furaldehyde was added. The mixture was then stirred for an additional 15 min and then quenched by being poured into an addition funnel containing 200 mL of saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed three times with 100-mL portions of saturated aqueous sodium bicarbonate and twice with 100-mL portions of saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. In vacuo removal of solvent afforded a 2.5:1 mixture of exo/endo aldol adducts in 95% yield. The mixture of adducts could be directly acetylated in the next step. A sample of the pure exo adduct was obtained by chromatography on silica (HPLC) using hexane/ethyl acetate (10:1) as the eluant: $[\alpha]_D$ = +55° (c = 0.01, $CHCl_3$); mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3 H), 1.10 (s, 3 H), 1.69 (m, 3 H), 1.93 (m, 1 H), 2.05 (d, J = 4, 1 H), 2.60 (d, J = 10, 1 H), 3.14 (d, J = 10, 1 H), 3.47 (d, J = 10, 1 H), 4.25 (s, 1 H), 4.87 (d, J = 10, 1 H), 6.30 (d, J = 3, 1 H), 6.35 (m, J = 3.0, 1.5, 1 H), 7.41 (d, J = 1.5 1 H); ^{13}C NMR δ 9.2, 18.7, 28.2, 28.8, 39.8, 43.8, 50.7, 57.1, 58.7, 69.3, 107.8, 110.1, 142.6, 153.6, 220.1; IR (cm^{-1}, KBr pellet), 3521, 3120, 2962, 2881, 1746, 1725, 1247, 1021, 751, 606; high resolution MS m/z (M+) calcd for $C_{15}H_{19}O_3Br$ 326.0513, found 326.0518.

Acetylation of the Exo/Endo (32 + Endo Isomer) Aldol Adduct Mixture. A 250-mL Erlenmeyer flask was charged with 20 mL (143.5 mmol) of Et_3N, 7.2 mL (76.45 mmol, 5 equiv) of acetic anhydride, and 0.1 g (0.76 mmol) of DMAP and cooled to 0 °C. To this was added dropwise a solution of 5.0 g (15.3 mmol) of the 2.5:1 exo/endo adduct mixture obtained from the previous reaction in 15 mL of CH_2Cl_2. The mxiture was allowed to stir for 10 min and 50 mL of cold water was added. The mixture was transferred to a separatory funnel. The layers were separated. The aqueous layer was extracted three times with 30-mL portions of Et_2O. The combined organic layers were washed successively two times with 30-mL portions of 5% HCl, two times with 30-mL portions of saturated aqueous $NaHCO_3$, three times with 40-mL portions of water, and once with saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded 5 g (90%) of a 2.5:1 mixture of the exo/endo acetates. Recrystallization with 2-propanol at −25 °C for 1–2 days gave 3.22 g (57%) of pure exo acetate **32**: $[\alpha]_D$ = +55° (c = 0.0028, $CHCl_3$); mp 142–143 °C; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.17 (s, 3 H), 1.59 (m, 3 H), 1.93 (m, 1 H), 2.01 (d, J = 4, 1 H), 2.11 (s, 3 H), 2.72 (d, J = 11, 1 H), 3.15 (d, J = 10, 1 H), 3.46 (d, J = 10, 1 H), 6.13 (d, J = 11, 1 H), 6.36 (d, 2 H), 7.42 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 9.5, 18.4, 20.9, 28.2, 29.3, 40.0, 44.3, 50.3, 54.2, 58.9, 67.8, 109.5, 110.3, 143.1, 151.1, 170.0, 214.2; IR (cm^{-1}, CCl_4) 3151, 2979, 1736, 1500, 1365, 1241, 1104, 1014, 933, 759; high resolution MS m/z calcd for $C_{17}H_{21}O_4Br$ 368.0638, found 368.0634.

Single-Step Aldol–Acetylation Procedure. The aldol reaction was carried out as in the above procedure up to the quenching step. For trapping of the intermediate aldol (from a reaction starting from 14.3 mmol of **18**), 2 mL of HMPA was added followed by 2.24 mL (31.5 mmol, 2.2 equiv) of acetyl chloride. The reaction was allowed to warm to 0 °C and worked up as in the regular aldol procedure to provide 6.84 g of crude aldol adduct acetates. Crystallization from 2-propanol yields 2.39 g of the pure exo acetate **32**.

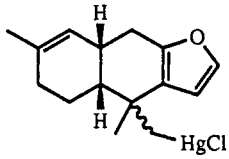
Fragmentation of 32 → 33. A 250-mL three-necked flask was charged with a solution of 3.5 g (9.46 mmol) of the exo acetate **32** in 100 mL of dry THF and cooled to −78 °C. The cold solution was titrated with ca. 75 mL (30 mmol, 3.2 equiv) of the 0.4 M Na–naphthalenide/0.4 M TGDE solution. When a deep green color persisted, 3 mL (17.2 mmol, 1.7 equiv) of HMPA and 2.1 mL (14.5 mol, 1.45 equiv) of diethyl phosphorochloridate were syringed in dropwise. The reaction was allowed to warm to −40 °C and quenched by the addition of 100 mL of saturated aqueous NH_4Cl. The solution was transferred to a 500-mL separatory funnel and the aqueous layer was extracted three times with 50-mL portions of Et_2O. The combined organic layers were washed three times with water and twice with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded a pale yellow solid containing the desired product and naphthalene. Flash column chromatography eluting first with 95:5 hexane/ethyl acetate and then with 70:30 hexane/ethyl acetate yielded 3.22 g (80%) of the desired enol phosphate **33**: $[\alpha]_D$ = +139° (c = 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (m, 6 H), 1.50 (s, 3 H), 1.70 (s, 3 H), 1.78 (overlapping m, 2 H), 1.96 (s, 3 H), 2.13 (overlapping m, 2 H), 2.38 (m, 1 H), 3.54 (m, 1 H), 4.09 (m, 4 H), 4.70 (s, 1 H), 4.75 (s, 1 H), 5.85 (d, J = 5, 1 H), 6.22 (m, 1 H), 6.24 (m, 1 H), 7.28 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.0, 16.3, 20.8, 21.6, 22.1, 29.9, 41.7, 44.1, 63.7, 67.2, 108.1, 110.2, 111.5, 122.3, 140.0, 141.6, 145.3, 153.1, 169.4; IR (cm^{-1}, neat) 3117, 3085, 2986, 2912, 1744, 1700, 1646, 1444, 1370, 1265, 1141, 1038, 970, 918, 751; high resolution MS m/z calcd for $C_{21}H_{30}O_6P$ (M^+) 426.1807, found 426.1810.

Reductive Cleavage of 33 → 34. A 250-mL three-necked flask equipped with a dry ice condenser and a pressure equalizing addition funnel was charged with a solution of lithium ammonia (ca. 0.16 g, 5 equiv of Li/30 mL of NH_3) at −78 °C. To this was added dropwise a solution of 2 g (4.7 mmol) of the enol phosphate in 6.4 mL (65.7 mmol, 14 equiv) of 2-propanol and 15 mL of dry THF. The reaction was stirred for 2 h at −78 °C, adding additional lithium when necessary to maintain the deep blue color of the solution. The reaction was allowed to warm slowly to room temperature and quenched (when gas evolution had ceased) by the addition of 10 mL of saturated NH_4Cl. The solution was transferred to a 250-mL separatory funnel and the layers were separated. The aqueous layer was extracted three times with 50-mL portions of Et_2O. The combined organic layers were washed twice with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 0.85 g (85%) of the desired limonene derivative **34**, which was used in the next step without further purification: $[\alpha]_D$ = +359° (c = 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.68 (s, 3 H), 1.70 (overlapping m, 2 H), 1.83 (s, 3 H), 2.06 (bs, 2 H), 2.33 (m, 2 H), 2.66 (m, 2 H), 4.77 (s, 1 H), 4.94 (s, 1 H), 5.42 (m, 1 H), 6.00 (d, J = 3, 1 H), 6.31 (dd, J = 2, 3, 1 H), 7.34 (d, J = 2, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.6, 23.4, 29.5, 30.7, 35.4, 43.6, 105.5. 110.0, 110.2, 124.8, 133.8, 140.6, 147.3, 155.5; IR (cm^{-1}, neat) 3084, 2965, 2926, 2833, 1644, 1595, 1504, 1441, 1377, 1145, 1010, 890, 723; high resolution MS m/z (M^+) calcd for $C_{15}H_{20}O$ 216.1519, found 216.1514.

(−)-Furodysinin ((−)-3a). A 50-mL flask was charged with 0.230 g (1.1 mmol) of **34** and 25 mL of dry CH_2Cl_2. The mixture was cooled to 0 °C and 0.55 g (1.7 mmol, 1.5 equiv) of $Hg(NO_3)_2$ was added. The mixture was allowed to warm slowly to room temperature and stirred for an additional 4 h. The mixture was then cooled back to 0 °C and 2.43 mL (ca. 11 mmol, 10 equiv) of a 12% wt solution of $NaBH_4$ in 14 N NaOH was added. The resulting solution was allowed to warm slowly to room temperature and stirred for an additional 2 h. The mixture was then filtered through Florisil and diluted with water. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed three times with 50-mL portions of saturated aqueous $NaHCO_3$ and three times with 50-mL portions of saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo afforded a discolored solid. This was chromatographed on silica using hexanes

as the eluant to separate the high R_f material containing (-)-**3a**. Chromatography of this fraction on silica (medium-pressure liquid chromatography) afforded 24 mg (10% yield) of colorless spears, which were spectroscopically identical, although opposite in optical rotation, with an authentic sample of natural (+)-furodysinin: $[\alpha]_D$ = -54° (c = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (s, 3 H), 1.19 (s, 3 H), 1.32 (overlapping m, 2 H), 1.66 (s, 3 H), 1.54 (bd, 1 H), 2.03 (m, 2 H), 2.29 (m, 1 H), 2.73 (m, 2 H), 5.57 (bs, 1 H), 6.24 (d, J = 2, 1 H), 7.21 (d, J = 2, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3, 23.1, 26.2, 27.6, 29.7, 31.3, 31.7, 33.9, 44.7, 108.2, 124.7, 126.2, 133.6, 140.5, 147.5; IR (cm^{-1}, KBr pellet) 2962, 2907, 2863, 1634, 1506, 1446, 1361, 1262, 1197, 1130, 1055, 1027, 897, 839, 799, 728; high resolution MS m/z (M^+ - H) calcd for $C_{15}H_{19}O$ 215.1435, found 215.1430.

Organomercurial Intermediate in the 44 → (-)-2a Conversion. This intermediate could be isolated in 14% yield by flash chromatography on silica, eluting with 2:1 hexane/CH_2Cl_2. Conversion of this substance to (-)-**2a** could be accomplished quantitatively by reduction with aqueous basic $NaBH_4$ solution. The organomercurial appears to be a 2:1 mixture of isomers at C1: ^1H NMR ($CDCl_3$) δ 7.22 (br s), 6.26 (br s), 5.61 (m), 2.74



(overlapping m), 2.30 (overlapping m), 2.07 (m), 1.80 (m), 1.67 (s), 1.49 (m), 1.67 (s), 1.49 (m), 1.34 (s), 1.32 (s); ^{13}C NMR ($CDCl_3$) δ 147.6, 141.4, 141.0, 133.8, 133.6, 125.6, 125.5, 124.1, 107.6, 107.5, 53.0, 47.5, 46.4, 38.3, 36.1, 31.7, 31.5, 31.3, 31.1, 29.5, 27.6, 23.1, 19.9, 19.7; IR (neat oil) 3143, 3103, 2964, 2911, 2858, 1629, 1503, 1463, 1443, 1384, 1198, 1131, 1058, 905, 733 cm^{-1}; low resolution mass spectrometry 215 ($C_{15}H_{19}O$, M^+ - HgCl).

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Registry No. (-)-**2a**, 129783-56-8; (-)-**3a**, 98672-90-3; **9**, 464-49-3; **10**, 129594-57-6; **14** (R = Me), 129594-67-8; **14** (R = Et), 129594-68-9; **14** (R = *i*-Pr), 129594-70-3; **14** (R = *t*-Bu), 129618-70-8; **14** (R = Ph), 60300-67-6; **14** (R = $PhCH_2$), 129594-74-7; **14** (R = 2-furyl), 129594-58-7; **15** (R = Me), 129704-48-9; **15** (R = Et), 129594-69-0; **15** (R = *i*-Pr), 129594-71-4; **15** (R = *t*-Bu), 129594-72-5; **15** (R = Ph), 129594-73-6; **15** (R = $PhCH_2$), 129594-75-8; **15** (R = 2-furyl), 129594-59-8; **18**, 10293-09-1; **20**, 5989-27-5; **21**, 129704-41-2; **22**, 129594-60-1; **23**, 129594-61-2; **24**, 129704-42-3; **25**, 129704-43-4; **26**, 129704-44-5; **27**, 129704-44-5; **28**, 28974-17-6; **29a**, 129704-46-7; **30a**, 20347-65-3; **30b**, 464-43-7; **30** (R = Ms), 129704-47-8; **31**, 122763-76-2; **32**, 122763-77-3; *endo*-**32**, 129594-78-1; **32** alcohol, 122763-80-8; *endo*-**32** alcohol, 129594-76-9; **33**, 122763-78-4; **34**, 122763-79-5; **35**, 129594-62-3; **36** (isomer 1), 129594-63-4; **36** (isomer 2), 129594-79-2; **42**, 129594-64-5; *endo*-**42**, 129594-77-0; **43**, 129594-65-6; **44**, 129594-65-6; MeCHO, 75-07-0; EtCHO, 123-38-6; *i*-PrCHO, 78-84-2; *t*-BuCHO, 630-19-3; PhCHO, 100-52-7; $PhCH_2CHO$, 122-78-1; 2-furaldehyde, 98-01-1; (+)-*endo*-3-bromocamphor, 10293-06-8; (+)-*endo*-3,9-dibromocamphor, 10293-10-4; 3-furaldehyde, 498-60-2.

Supplementary Material Available: Proton and ^{13}C spectral data on all synthetic intermediates (34 pages). Ordering information is given on any current masthead page.

On the Diastereofacial Selectivity of Lewis Acid Catalyzed Carbon–Carbon Bond Forming Reactions of Conjugated Cyclic Enones Bearing Electron-Withdrawing Substituents at the γ-Position

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Lewis acid catalyzed reactions of several cyclic enones are described. The γ-OTBS enones **1** and **2** give products where carbon–carbon bond formation at the β carbon occurs with high stereoselectivity favoring attack syn to the resident OTBS group. In the case of enone **24** bearing an additional dioxolane ring, the products correspond to addition anti to the resident carbon–oxygen bond at the γ carbon. The reaction of **24** with lithium dimethylcuprate also occurs in an anti sense. The starting materials in this study are available in quantity in optically pure form. Given the excellent stereoselectivity of the reactions, these compounds are useful intermediates for synthesis.

Introduction

Recently we had occasion to study Lewis acid catalyzed Michael-type addition reactions of silyl ketene acetals to the γ-OTBS cyclenones **1**[1] and **2**.[2] In each instance, carbon–carbon bond formation was accompanied by group transfer of the silyl function.[3,4] The resultant silyl enol ethers, reacted with suitable aldehydes in highly stereoselective reactions to produce products that lent themselves to conversion to prostaglandin $F_{2\alpha}$[1,5] and compactin,[2,6] respectively (Scheme I).

(1) Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456.
(2) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599.
(3) Webster, O. W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. B.; Rajan Babu, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 5706.
(4) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 1805.
(5) See also: Chow, K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 6016.
(6) Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1155.

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