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Synthesis of (−)-Nakamurol A and Assignment of Absolute Configuration of Diterpenoid (+)-Nakamurol A

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Received June 17, 2003

The total synthesis of the enantiomer of the marine sponge diterpenoid nakamurol A and determination of the absolute configuration of this natural product are reported. This first synthetic entry to thelepogane-type diterpenoids involves the use of the bicyclic enone (−)-**3**, which after a tandem difunctionalization process and elongation of the side chain leads to the formation of the ketone (−)-**13**. From (−)-**13**, two approaches to *ent*-nakamurol A (**1**) are reported: the straightforward but nonselective way, by reaction with vinylmagnesium bromide, and a longer but stereocontrolled route, through the primary allylic alcohol **20**, which is submitted to a Sharpless epoxidation followed by a tellurium-promoted reductive-epoxide ring-opening cascade reaction.

Introduction

Marine sponges *Agelas nakamurai* have proved to be rich sources of unusual diterpenoids with interesting biological activities as well as unique structures. Nakamurol A was isolated from *Agelas nakamurai* Hoshino collected from Okinawa island and its structure elucidated in 1996[1] (Figure 1), although neither its relative configuration at C(13) nor its absolute configuration was established. The diterpenoid nakamurol A is made up of a *cis*-decalin embodying four contiguous stereogenic centers and a side chain containing an allylic tertiary alcohol. Its previously unknown skeletal arrangement,[2] which has been named thelepogane due to its similarity with the alkaloid thelepoghine,[3] is related to that of labdanes [Me(19) is linked at C(5) instead of C(4)] and clerodanes [Me(20) is linked at C(10) instead of C(9)].[4] Interestingly, this particular backbone of the *cis*-decalin unit, which contains side chains at C(4), C(5), C(8), C(9), and C(10), is also found in a family of natural products isolated from *Aspergillius* sp.[5]

In this paper, we describe the first total synthesis of (−)-nakamurol A,[6] which constitutes the first synthetic entry to the thelepogane skeleton and allows the relative configuration at C(13) and the absolute configuration of the natural product (+)-nakamurol A to be established. Our synthetic planning (Scheme 1) was based on the use of the enantiopure bicyclic enone **I** as the advanced synthetic intermediate, which not only ensures a known configuration for the two stereogenic centers at C(4) and C(5)[7] but could also allow good stereocontrol in the genesis of the stereogenic centers at C(9) and C(10) through a tandem vicinal difunctionalization. Subsequent elaboration of the side chain and a methylenation would afford the methyl ketone **II**, from which a stereoselective elaboration of the tertiary allylic alcohol should be carried out to achieve nakamurol A.

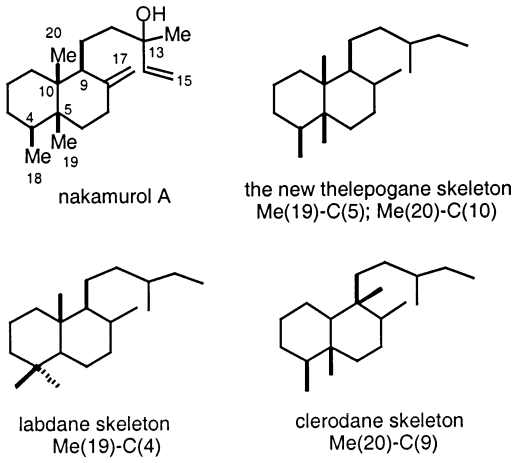


FIGURE 1. Thelepogane, labdane, and clerodane skeletal diterpene types.

Results and Discussion

As point of departure for the synthesis of nakamurol, the commercially available (*R*)-3-methylcyclohexanone

(1) Shoji, N.; Umeyama, A.; Teranaka, M.; Arihara, S. *J. Nat. Prod.* **1996**, *59*, 448−450.

(2) A compound with the same bicyclic skeleton possesing a 9-methyladenium moiety in the side chain was later isolated: Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M.; van Soest, R. W. M. *J. Nat. Prod.* **1998**, *61*, 1310−1312.

(3) Thelepogine, isolated from the terrestrial grass *Thelepogan elegans*, is the only diterpenoid alkaloid with this backbone reported so far: Crow, W. D. *Aust. J. Chem.* **1962**, *15*, 159−161.

(4) For reviews in this field, see: (a) Tokoroyama, T. *Synthesis* **2000**, 611−633. (b) Klein Gebbinck, E. A.; Jansen, B. J. M.; de Groot, A. *Phytochemistry* **2002**, *61*, 737−770.

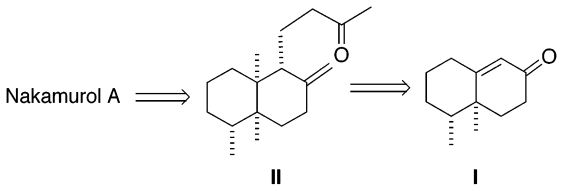
(5) Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343−350.

(6) For our preliminary studies in the racemic series, see: Bonjoch, J.; Cuesta, J.; Díaz, S.; González, A. *Tetrahedron Lett.* **2000**, *41*, 5669−5672.

(7) Throughout the discussion, the numbering of the nakamurol skeleton is followed as given by Umeyama in ref 1.

10.1021/jo034838r CCC: $25.00
Published on Web 08/21/2003

SCHEME 1. Retrosynthesis of Nakamurol



was converted to the enantiopure Piers' enol lactone **2** following our previously reported procedure.[8] Treatment of **2** with the lithium salt of the dimethyl methylphosphonate[9] gave the bicyclic enone (−)-**3**[10,11] in 60% yield (75% based on consumed material), which was a reliable alternative to the original protocol that used methyllithium as the nucleophile for the cleavage of the enol lactone **2** giving a methyl ketone that had to be submitted to an aldol process.[8]

According to our synthetic plan, to build the required all-cis tetrasubstituted decalone from ketone **3**, it was necessary to introduce the methyl group C(20) by a conjugate addition and trap the enolate[12] by a reagent that furnishes a functionality that would allow further elaboration of the side chain at C(9) (Scheme 2). Initially, we explored the dimethyl cuprate reagent for the generation of the quaternary center at C(10)[13] and used methyl bromopropionate for quenching, but only the trimethyldecalone **4** (Figure 2) was isolated.[14] So, to obtain the α-functionalization, we then tried a more electrophilic reagent such as formaldehyde to trap the enolate[15] generated after the β-addition to the α,β-unsaturated ketone **3**. Although the desired alcohol **5** was isolated, using $Me_2CuLi{\cdot}MeS$ in the first step, the result was not always reproducible (the yields ranged from 15 to 60%) and even the 1,2-adduct was formed in some runs. In contrast, exposure of bicyclic enone **3** to the $ZnMe_2-Ni(acac)_2$[16] gave keto alcohol **5** in reproducible 52% yield after the enolate was captured with gaseous formaldehyde. The process was stereoselective since **5** is a single diastereomer, whose stereochemistry was inferred from

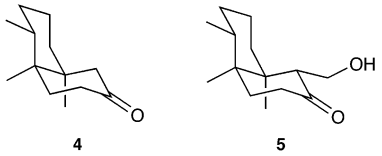
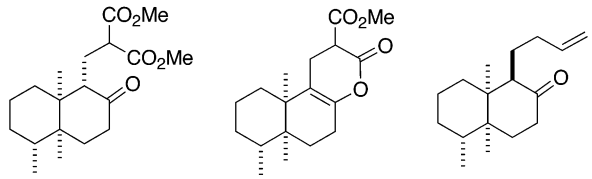


FIGURE 2. Preferred conformation of **4** and **5**.

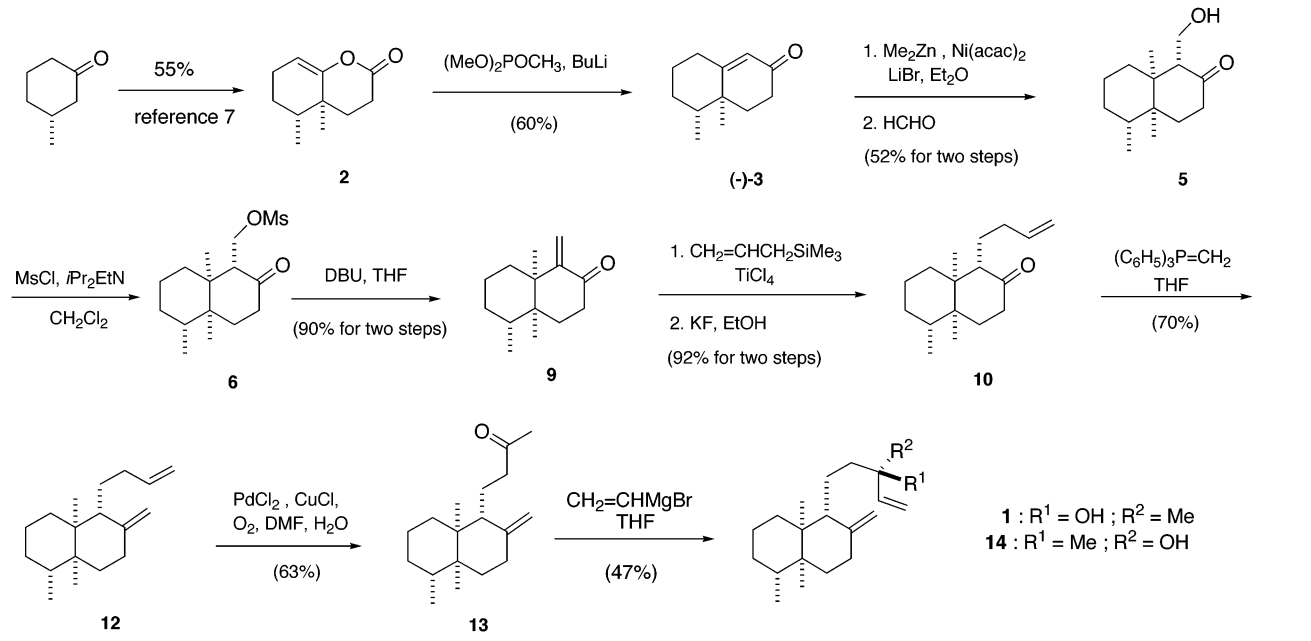
the NMR spectral data, which allowed the configuration as well as the preferred conformation for this decalone to be determined. The most noteworthy data in the ^{13}C NMR spectrum of **5** were the chemical shift of C-2[7] (δ 21.4), which is a diagnostic value for the cis-fused decalone ring,[17] and that of C-1 (δ 31.8), which is shifted upfield by the hydroxymethyl substituent, equatorially located at C-9 with a 1,3-relationship with the H-1eq (in the C-9 unsubstituted derivative, C-1 resonates at δ 35.9).

For the elongation of the carbon chain from the primary alcohol group of **5**, we first attempted an alkylation process by treating the corresponding mesylate **6** with the sodium salt of the dimethyl malonate, which afforded a mixture of the desired diester **7** (33%) and the enol lactone **8** (14%) as an epimeric mixture. After this unfruitful result, we decided to again temporarily sacrifice the stereogenic center at C(9), working from enone **9** to construct the 3-hydroxy-3-methyl-4-pentenyl side chain at C(9).



Mesylation of alcohol **5** followed by an elimination process induced by DBU gave α-methylene ketone **9**. The problem foreseen in the use of the α-methylene ketone **9** for this synthesis was the known susceptibility of such a

SCHEME 2. Synthesis of (−)-Nakamurol A (1)



system toward Diels−Alder-type dimerization.[18] However, treatment of freshly prepared enone **9** with allyltrimethylsilane (2.5 equiv) and $TiCl_4$ (1 equiv), according to the usual protocol for a Sakurai reaction,[19] afforded keto alkenes **10** and **11** in 94% yield as a 3:2 mixture of C-9 epimers enriched in the desired isomer. Although adjusting the reaction conditions had little impact on this ratio, it was possible to equilibrate the mixture to achieve adequate all-cis stereochemistry. Thus, exposure of a mixture of epimers **10** and **11** to KF in refluxing ethanol over a period of 48 h led to pure **10**, showing the butenyl side chain equatorially located. The signal for H-9_{ax}, in the ^{1}H NMR spectrum, allowed the stereochemical assignment for **10** either from its multiplicity (doublet) and coupling constants or its NOESY interrelationhips, especially with the axial protons at H-2, H-4, and H-7. Moreover, since this signal appeared to be isolated in the NMR spectrum of the mixture of epimers **10** and **11**, it can be used as a pattern for a quick evaluation of the ratio of isomers after the Sakurai reaction. As observed in compound **5** (see above), the upfield-shifted signal of C(1) in the ^{13}C NMR spectrum of **10** corroborated its stereostructure. The transformation of ketoalkene **10** to the target diterpenoid was accomplished as outlined. Wittig olefination of **10** afforded the bisalkene derivative **12**, which was oxidized chemoselectively under the Wacker conditions ($PdCl_2$, CuCl, O_2) to afford the methyl ketone **13** in convenient yield.[20] Finally, reaction of **13** with vinylmagnesium bromide gave a 1.2:1 mixture of **1** and its C-13 epimer **14** (vide infra),[21] but unfortunately this mixture could not be separated by chromatography. Although the ^{1}H NMR spectroscopic data for the major isomer formed were consistent with those reported for the natural product, it was not possible to assign either the absolute configuration of nakamurol A or unequivocally the configuration at C(13) of the major component of the epimeric mixture.[22]

A careful analysis of the ^{1}H NMR spectrum of the mixture of epimers **1** and **14** allowed us to carry out a tentative assignment of the configuration of C(13) in both compounds and hence propose the relative configuration of nakamurol A. The stereochemical assignment of C(13) for **1** and its epimer **14** was based specifically on the chemical shifts of the vinyl protons at C(17) in the two isomers. These protons were observed at a lower field and with a smaller $\Delta\delta$ between them in compound **1**, trends that have been consistently observed for related labdane diterpenoids with a (*S*,*S*)- relationship for the stereogenic centers at C(9) and C(13), when compared with their epimers of (13*R*)-configuration (see Table 2 in Supporting Information).[21,23,24] Consequently, considering that compound **1** has a (9*R*)-configuration, since we are working in the enantiomeric series with respect to manool and related labdane diterpenoids, the (13*R*)-configuration was assigned for **1**. In summary, taking into account all data reported so far about labdane diterpenoids that incorporate a 3-hydroxy-3-methyl-4-pentenyl group at C(9) and a methylene goup at C(17), the NMR signals of the latter vinylic protons can be used for the assignment of the configuration of the C(13) of natural compounds if the NMR data of both epimers are available.

We then decided to explore other synthetic approaches with the aim of diastereoselectively obtaining the allylic alcohol of the side chain of nakamurol A in order to achieve exclusively compound **1**. We briefly examined the possibility of employing sulfone **17** as the platform for introducing the side chain of the target compound,[25] since the addition of the α-carbanion of **17** to (3*R*)-isoprene oxide[26] could produce **1**. Initially, we addressed the preparation of the key sulfone intermediate **17** (Scheme 3) by conjugate addition of thiophenol[27] to the α,*β*-unsaturated ketone **9** followed by Wittig olefination of keto sulfide **15** and chemoselective oxone oxidation of **16**. Alternatively, sulfone **17** was synthesized by oxidation of **15** followed by a nonbasic methylenation of the ketone

(8) Cuesta, X.; González, A.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3365−3370.

(9) For the application of this method to the synthesis of α-vetivone, see: Revial, G.; Jabin, I.; Pfau, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4975−4983. See also: Revial, G.; Jabin, I.; Redolfi, M.; Pfau, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1683−1688.

(10) For another synthesis of (−)-**3**, see: Schenato, R. A.; dos Santos, E. M.; Tenius, B. S. M.; Costa, P. R. R.; Caracelli, I.; Zukerman-Schpector, J. *Tetrahedron: Asymmetry* **2001**, *12*, 579−584.

(11) Synthesis of (+)-**3** has been described from the Wieland−Mischer ketone (Paquette, L. A.; Wang, T.-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367−3374) and from carvone (Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073−10082).

(12) For a review about tandem vicinal difunctionalization of α,*β*-unsaturated carbonyl substrates, see: Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225−653.

(13) For studies of organocuprates with bicyclic rigid α,*β*-unsaturated ketones, see: Vellekoop, A. S.; Smith, R. A. J. *Tetrahedron* **1998**, *54*, 11971−11994 and references therein.

(14) Compound **4** has been previously reported, but without NMR characterization: Cory, R. M.; Burton, L. P. J.; Chan, D. M. T.; McLaren, F. R.; Rastall, M. H.; Renneboog, R. M. *Can. J. Chem.* **1984**, *62*, 1908−1921.

(15) For a related tandem process, see: Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M.; Iio, H. *Tetrahedron* **1988**, *44*, 6607−6622.

(16) For the use of these reagents in related processes, see: (a) Luche, J. L.; Petrier, C.; Lansard, J. P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837−3839. (b) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2787−2790. (c) Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467−5480.

(17) For ^{13}C NMR studies in *cis*-10-methyl-2-decalones, see: (a) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Org. Magn. Reson.* **1979**, *12*, 561−568. (b) Gramain, J. C.; Quirion, J. C. *Magn. Reson. Chem.* **1986**, *24*, 938−946. (c) Di Maio, G.; Migneco, L. M.; Vecchi, E.; Iavarone, C. *Magn. Reson. Chem.* **2000**, *38*, 108−114.

(18) For examples of dimerization of enones in the steroid field, see: (a) Romann, E.; Frey, A. J.; Stadler, P. A.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1900−1917. (b) DellaGreca, M.; Monaco, P.; Previtera, L.; Zarrelli, A.; Fiorentino, A.; Giordano, F.; Mattia, C. A. *J. Org. Chem.* **2001**, *66*, 2057−2060.

(19) This methodology for the elaboration of the side chain [C(11)−C(16)] has been studied in the synthesis of *rac*-nakamurol A; see ref 6.

(20) For a similar approach in the synthesis of copalol, see: Toshima, H.; Oikawa, H.; Toyomasu, T.; Sassa, T. *Tetrahedron* **2000**, *56*, 8443−8450.

(21) Same epimeric ratio has been previously noted in the manool-related labdane diterpenes: Yasui, K.; Kawada, K.; Kagawa, K.; Tokura, K.; Kitadokoro, K.; Ikenishi, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1698−1707.

(22) Due to the dearth of the natural product (personal communication of Prof. A. Umeyama, University of Tokyo) we were unable to obtain a sample of nakamurol A for chromatographic comparisons.

(23) Barrero, A. F.; Sánchez, J. F.; Alvarez-Manzaneda, E. J.; Muñoz Dorado, M.; Haidour, A. *Phytochemistry* **1993**, *32*, 1261−1265.

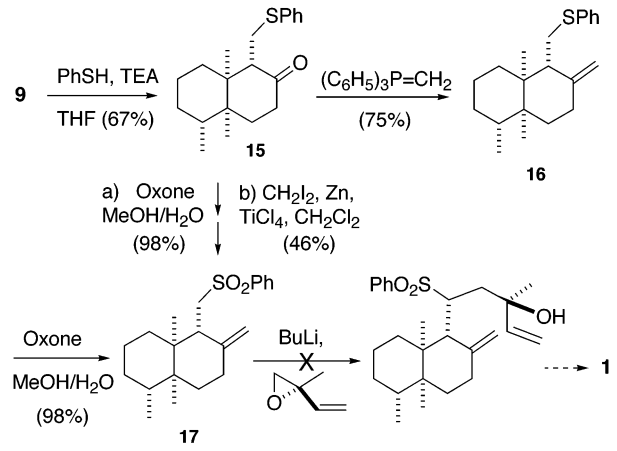
(24) Kagawa, K.; Tokura, K.; Uchida, K.; Kakushi, H.; Shike, T.; Kikuchi, J.; Nakai, H.; Dorji, P.; Subedi, L. *Chem. Pharm. Bull.* **1993**, *41*, 1604−1607.

(25) For a seminal work, see: Cane, D. E.; Yang, G. *J. Org. Chem.* **1994**, *59*, 5794−5798.

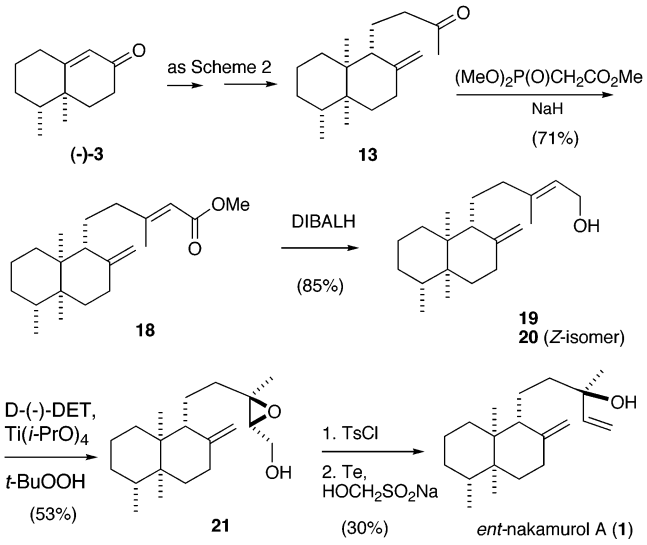
(26) Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599−2601.

(27) Tamura, R.; Watabe, K.; Kamimura, A.; Hori, K.; Yokomori, Y. *J. Org. Chem.* **1992**, *57*, 4903−4905.

SCHEME 3. Studies through Sulfone 17



SCHEME 4. Stereocontrolled Synthesis of *ent*-Nakamurol A



group,[28] although the overall yield was lower than in the aforementioned sequence**.** Unfortunately, sulfone **17** proved to be an unusually inert compound and thus was recovered unchanged after treatment with different basic reagents and (3*R*)-isoprene oxide. On the other hand, attempts to generate the corresponding lithium derivative from the ethylene acetal of sulfide **15** (not shown) or sulfide **16** by reaction with LDBB (lithium 4,4′-di-*tert*-butylbiphenylide)[29] and coupling with the (3*R*)-isoprene epoxide in each case resulted only in the recovery of the starting sulfide.

Second Generation Synthesis of Nakamurol A (1). We finally directed our efforts toward enantiopure **1** using the reductive ring-opening of the epoxide **21** (Scheme 4). For this purpose we chose as a precursor the methyl ketone **13**, used in the first approach. The elongation of the side chain[30] was accomplished by

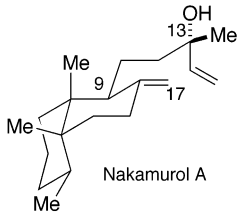


FIGURE 3. Structure of nakamurol A.

treating **13** with the sodium salt of trimethyl phosphonoacetate in THF to give a 5:1 mixture of the chromatographically nonseparated diastereomers (*E*)-unsaturated ester **18** and its (*Z*)-isomer. However, this was not a major problem since the corresponding products formed from each diastereomer were easily separated in the next step of the synthesis. Thus, the reduction of the mixture of **18** and its (*Z*)-isomer with DIBALH[31] provided the pure allylic alcohol **19** (60% overall yield from **13**) needed for the asymmetric epoxidation, the alcohol **20** also being isolated as the minor isomer. Stereoselective epoxidation of the allylic alcohol **19** by the asymmetric Sharpless method[32] using D-(−)-diethyl tartrate (DET) gave the desired (13*R*,14*R*)-epoxide **21** in 53% yield after removal of the minor epoxide diastereomer (dr = 9:1). The (13*R*,-14*R*)-stereochemistry of the major diastereomer **21** was assigned on the basis of the expected reagent-directed epoxidation preference,[33] as well as from the NOESY data from its 600 MHz spectrum. To obtain the tertiary allylic alcohol **1** from **21**, the latter was transformed into the corresponding tosylate, which was treated with Te in the presence of rongalite ($HOCH_2SO_2Na$) in aqueous medium. This procedure generated Te^{2-}, which induces an initial S_N upon tosylate followed by an opening of the epoxide ring, forming an *epi*-telluride, which loses elemental Te.[34,35] After this stereocontrolled process, compound **1** was isolated, showing ^1H and ^{13}C NMR spectroscopic data identical to those reported for the natural product. All that remained to establish the absolute stereochemistry of natural nakamurol A was to measure the optical rotation of the synthetic nakamurol A (**1**). The data obtained, $[\alpha]_D = -36.3$ (c = 0.02, $CHCl_3$) for **1**, resulted in the assignment of the *ent*-nakamurol A for **1** and the shown (4*S*,5*R*,9*S*,10*R*,13*S*)- absolute configuration for the natural (+)-nakamurol A [Lit[1] $[\alpha]_D$ +39.1 (c 1.6, $CHCl_3$)] (Figure 3). Both the enantioselective total synthesis of *ent*-nakamurol A and the assignment of its absolute configuration were thus achieved.

In conclusion, the first total synthesis of *ent*-nakamurol A (**1**) was achieved in 16 steps and 3% overall yield (together with **14**) from (−)-3-methylcyclohexanone. A

(28) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579−5580.
(29) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569−11584.
(30) For an alternative process to convert a side chain from 3-oxobutyl to 5-hydroxy-3-methyl-3-pentenyl in the terpene field, see: Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rodríguez Rivas, A.; Linares Palomino, P. *Tetrahedron* **2000**, *56*, 6099−6113.
(31) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250−8257.
(32) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780 and references therein.
(33) (a) Pfenninger, A. *Synthesis* **1986**, 89−116. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1−299.
(34) (a) Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718−731. (b) Kumar, A.; Dittmer, D. C. *Tetrahedron Lett.* **1994**, *35*, 5583−5586.
(35) For an alternative procedure, working through the corresponding iodide, to convert epoxy tosylates upon tertiary allylic alcohols, see: (a) Nicolaou, K. C.; Duggan, M. E. *Tetrahedron Lett.* **1984**, *25*, 2069−2072. (b) Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461−4472.

second-generation total synthesis of **1**, in which the C(13) stereocenter was established using catalyst rather than substrate control, was slightly longer but furnished **1** stereoselectively without forming its epimer **14**. These two syntheses are the first to be reported for a diterpenoid with the thelepogane-type skeleton and have allowed the absolute configuration of nakamurol A to be established.

Experimental Section[36]

(4a*S*,5*R*)-4a,5-Dimethyl-4,4a,5,6,7,8-hexahydro-3*H*-naphthalen-2-one (−)-3. *n*-BuLi (1.6 M in hexanes, 7.5 mL, 12.3 mmol) was added dropwise to a cooled (−78 °C) solution of dimethyl methylphosphonate (1.25 mL, 14 mmol) in THF (20 mL). After 5 min, a solution of lactone **2** (740 mg, 4.11 mmol) in THF (20 mL) was added, the temperature was raised to −20 °C and the stirring maintained for 6 h. The solution was poured into water−Et_2O, and the aqueous layer was extracted with Et_2O. The organic extracts were dried and concentrated, and the residue was purified by chromatography (from hexane to 98:2 hexane/EtOAc) to give **3**[8] (437 mg, 60%). When, after the ethereal extraction, the aqueous layer was acidified with 6 N HCl and extracted with Et_2O, 160 mg of the (1*S*,2*R*)-1,2-dimethyl-6-oxocyclohexanepropionic acid,[7] the synthetic precursor of enol lactone **2**, were recovered.

(1*R*,4a*S*,5*R*,8a*S*)-1-Hydroxymethyl-4a,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (5). Me_2Zn (2 M in toluene, 3.36 mL, 6.7 mmol) was added dropwise to a cooled (0 °C) dispersion of LiBr (1.17 g, 13.5 mmol) and $Ni(acac)_2$ (17 mg, 0.067 mmol) in Et_2O (9 mL). After the mixture was stirred for 5 min, a solution of **3** (300 mg, 1.68 mmol) in Et_2O (9 mL) was added dropwise, and the stirring was maintained for 24 h at room temperature. The mixture was cooled at −20 °C and exposed to a stream of formaldehyde gas that was passed through it for 30 min. After being allowed to reach room temperature, the reaction mixture was stirred for 1 h, poured into 10% aqueous NH_4Cl solution and Et_2O, and filtered through Celite, after which the filter pad was washed with Et_2O. The resulting two-phase mixture was separated and the aqueous layer extracted with Et_2O, and the organic extracts were washed with water and brine. The concentrated dried organic extracts were purified by chromatography (from hexane to 5% EtOAc/hexane) to give **5** (268 mg, 72%): $[\alpha]_D$ −17.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, COSY) δ 0.64 (s, Me-20), 0.73 (s, Me-19), 0.81 (d, J = 7 Hz, Me-18), 1.26−1.38 (m, 3H, H-1 and H-3), 1.45−1.53 (m, 3H, H-2 and H-3), 1.61 (td, J = 14.5, 4.8 Hz, H-6_{ax}), 1.80 (ddd, J = 14.5, 7, 2.5 Hz, H-6_{eq}), 2.12 (dq, J = 14.5, 4.5 Hz, H-7_{eq}), 2.27 (dqd, J = 12, 7.5, 5 Hz, H-4), 2.35 (tdd, J = 14.5, 6.6, 1 Hz, H-7_{ax}), 2.48 (br, OH), 3.12 (dd, J = 9, 3 Hz, H-9), 3.43 (dd, J = 11.5, 3.5 Hz, 1H, H-11), 3.90 (dd, J = 11.5, 9.0 Hz, 1H, H-11); ^{13}C NMR (75 MHz, HSQC) δ 15.2 (C-19), 16.3 (C-18), 19.7 (C-20), 21.4 (C-2), 30.3 (C-3), 30.7 (C-4), 31.8 (C-1), 32.2 (C-6), 38.0 (C-7), 39.1 (C-5), 44.6 (C-10), 53.5 (C-9), 58.3 (C-11), 216.2 (C-8); HRMS calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1782.

(4a*S*,5*R*,8a*R*)-4a,5,8a-Trimethyl-1-methylene-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (9). A cooled (0 °C) solution of **5** (133 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) was treated sequentially with *i*-Pr_2EtN (0.2 mL, 1.2 mmol) and methanesulfonyl chloride (0.08 mL, 0.9 mmol). After being stirred at room temperature for 4 h, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were washed with 0.5 N HCl and saturated aqueous $NaHCO_3$, dried, and concentrated to give the mesylate **6**, which was used in the next step without additional purification: ^{1}H NMR (200 MHz) δ 0.70 (s, 3H), 0.84 (s, 3H), 0.92 (d, J = 10 Hz, 3H), 3.08 (s, 3H), 3.45 (dd, J = 8.4, 2.2 Hz, 1H), 4.18 (dd, J = 9.6, 2.6 Hz, 1H), 4.62 (dd, J = 9.6, 8.4 Hz, 1H).

A solution of the above mesylate **6** (175 mg) in THF (10 mL) was treated with DBU (0.2 mL, 1.3 mmol) and heated at reflux for 15 h. The reaction mixture was cooled to room temperature and diluted with Et_2O, and the organic layer was washed with 2 N HCl. The dried organic extracts were concentrated and purified by chromatography (5% EtOAc/hexane) to give **9** (120 mg, 98% from alcohol **5**): $[\alpha]_D$ −31.6 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.83 (d, J = 6.9 Hz, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.4−1.53 (m, 4H), 1.67−1.87 (m, 5H), 2.41 (m, 2H), 5.28 (d, J = 1.5 Hz, 1H), 6.06 (d, J = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, DEPT) δ 15.7 (2q), 21.5 (t), 27.2 (q), 28.9 (t), 30.4 (t), 32.2 (t), 32.6 (d), 35.3 (t), 38.3 (s), 44.8 (s), 120.5 (t), 152.4 (s), 203.2 (s); HRMS calcd for $C_{28}H_{24}O_2$ (the dimer species)[17] 412.3341, found 412.3331.

(1*S*,4a*S*,5*R*,8a*S*)-1-(But-3-enyl)-4a,5,8a-trimethyl-3,4,4a,5,6,7,8,8a-octahydro-1*H*-naphthalen-2-one (10). A cooled (−78 °C) solution of enone **9** (100 mg, 0.48 mmol) in CH_2Cl_2 (3 mL) was treated sequentially with $TiCl_4$ (0.06 mL, 0.49 mmol) and allyltrimethylsilane (0.2 mL, 1.25 mmol). After the mixture was stirred at −78 °C for 3 h, the reaction was quenched by addition of water (1 mL) and allowed to reach room temperature. The resulting two-phase mixture was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by chromatography (1% EtOAc/hexane) to afford a 3:2 mixture of **10** and its epimer **11** (110 mg, 94%). A solution of this mixture in EtOH (15 mL), containing KF (418 mg, 7.2 mmol), was heated at reflux for 72 h. EtOH was removed, the residue dissolved in CH_2Cl_2, and the solution washed with water. The organic layer was dried and concentrated to give quantitatively enantiopure (+)-**10**: $[\alpha]_D$ +16.5 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, COSY, NOESY) δ 0.66 (s, 3H, Me-20), 0.82 (s, 3H, Me-19), 0.90 (d, J = 6.6 Hz, 3H, Me-18), 1.18 (m, 1H, H-2_{eq}), 1.36−1.47 (m, 3H, H-1. H-3), 1.47−1.50 (m, 3H, H-2_{ax}, H-11. H-12), 1.56 (dm, J = 9.5 Hz, 1H, H-3_{eq}), 1.67, (td, J = 14.5, 4.5 Hz, 1H, H-6_{ax}), 1.86 (m, 1H, H-11), 1.89 (ddd, J = 14, 4, 2 Hz, 1H, H-6_{eq}), 2.16 (ddd, J = 14, 4.5, 2 Hz, 1H, H-7_{eq}), 2.18 (m, 1H, H-12), 2.40 (m, 1H, H-4), 2.45 (td, J = 14.5, 6 Hz, 1H, H-7_{ax}), 2.98 (d, J = 9.5 Hz, H-9_{ax}), 4.95 (d, J = 11 Hz, 1H, H-16), 4.98 (d, J = 18 Hz, 1H, H-16), 5.78 (m, 1H, H-13); ^{13}C NMR (75 MHz, HSQC) δ 16.0 (C-18), 16.5 (C-19), 18.9 (C-20), 21.6 (C-2), 21.7 (C-11), 30.7 (C-3), 30.9 (C-4), 32.2 (C-6), 33.3 (C-1), 33.4 (C-12), 38.6 (C-7), 39.4 (C-5), 46.4 (C-10), 50.6 (C-9), 114.8 (C-16), 139.0 (C-13), 213.6 (C-8); HRMS calcd for $C_{17}H_{28}O$ 248.2140, found 248.2147

(1*R*,4a*S*,5*R*,8a*S*)-1-(But-3-enyl)-2-methylene-4a,5,8a-trimethyldecahydronaphthalene (12). To a dispersion of methyltriphenylphosphonium bromide (1.6 g, 4.63 mmol) in THF (3 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 2.8 mL, 4.63 mmol), and the mixture was stirred for 1 h. A solution of ketone **10** (115 mg, 0.46 mmol) in THF (2 mL) was added, and the reaction was heated at reflux for 16 h. After the mixture was cooled to room temperature, the reaction was quenched with water, and the aqueous layer extracted with EtOAc. The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (hexane) gave **12** (90 mg, 79%): bp (135 °C, 0.2 mbar); $[\alpha]_D$ −28.7 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, COSY) δ 0.63 (s, 3H, Me-20?), 0.74 (s, 3H, Me-19?), 0.79 (d, J = 7.2 Hz, 3H, Me-18), 1.25 (m, 1H, H-3), 1.30 (m, 1H, H-6_{ax}), 1.40 (m, 3H, H-1, H-2), 1.45 (m, 3H, H-3, H-11), 1.50 (m, 1H, H-1), 1.59 (dm, J = 14 Hz, 1H, H-6_{eq}), 1.91 (td, J = 16.5, 7.2 Hz, 1H, H-7_{ax}), 2.05 (dq, J = 13.2, 2.8 Hz, 1H, H-12), 2.17 (m, 1H, H-12), 2.25 (m, 1H, H-7), 2.34 (m, 1H, H-4), 2.64 (d, J = 9.6 Hz, 1H, H-9), 4.49 (d, J = 1.2 Hz, 1H, H-17), 4.84 (d, J = 1.6 Hz, 1H, H-17), 4.94 (d, J = 10.4 Hz, 1H, H-16), 4.99 (d, J = 17.2 Hz), 5.83 (ddt, J = 17.2, 10.4, 6.6 Hz, 1H, H-13); ^{13}C NMR (75 MHz, HSQC) δ 16.4 (C-18), 16.5 (C-19), 18.4 (C-20), 21.4 (C-2), 23.6 (C-11), 30.4 (C-4), 31.2 (C-3), 31.9 (C-1), 32.8 (C-7), 33.0 (C-12), 33.9 (C-6), 39.5 (C-5), 41.9 (C-9), 42.1 (C-10), 106.2

(36) Terpene numbering was used in the NMR assignation of all compounds, and the IUPAC nomenclature is followed in the headings.

(C-17), 114.1 (C-16), 139.5 (C-13), 149.3 (C-8); HRMS calcd for $C_{17}H_{27}$ (M-15) 231.2113, found 231.2112.

(1*R*,4a*S*,5*R*,8a*S*)-2-Methylene-1-(3-oxobutyl)-4a,5,8a-trimethyldecahydronaphthalene (13). A suspension of CuCl (20 mg, 0.20 mmol) and $PdCl_2$ (8 mg, 0.04 mmol) in DMF (0.5 mL) and H_2O (0.13 mL) was saturated with oxygen and stirred at 45 °C for 90 min. A solution of alkene **12** (33 mg, 0.13 mmol) in DMF (0.5 mL) was added, and the reaction was stirred under an oxygen atmosphere at 45 °C for 20 h. The mixture was poured into 3 N HCl and extracted with CH_2Cl_2. The organic layer was filtered through Celite, after which the filter pad was washed with hexane. The filtrate was dried and concentrated, and the residue was purified by chromatography (1% EtOAc/hexane) to afford **13** (25 mg, 71%): $[\alpha]_D$ −29.4 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, COSY) δ 0.65 (s, 3H, Me-20), 0.74 (s, 3H, Me-19), 0.78 (d, J = 7 Hz, 3H, Me-18), 1.23−1.60 (m, 9H), 1.75 (dddd, J = 13, 11.5, 7, 2 Hz, H-11), 2.03 (ddd, J = 13, 4.5, 2.5 Hz, H-7$_{eq}$), 2.10 (s, 3H, H-16), 2.14 (td, J = 13.5, 4 Hz, H-7$_{ax}$), 2.27(m, H-4), 2.33 (ddd, J = 17, 9.5, 7 Hz, 1H, H-12), 2.57 (br d, J = 11.5 Hz, H-9), 2.62 (ddd, J = 17.5, 9.5, 4.5 Hz, H-12), 4.40 (d, J = 1 Hz, 1H, H-17), 4.84 (d, J = 1.5 Hz, 1H, H-17); ^{13}C NMR (75 MHz, HSQC) 16.4 (C-18 and C-19), 18.1 (C-11), 18.2 (C-20), 21.3 (C-2), 30.1 (C-16), 30.5 (C-4), 31.1 (C-3), 31.9 (C-1), 33.1 (C-7), 34.0 (C-6), 39.5 (C-5), 42.2 (C-9), 42.4 (C-10), 43.0 (C-12), 106.3 (C-17), 149.2 (C-8), 209.0 (C-13). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.02; H, 11.71.

(3*R*)- and (3*S*)-5-[(1*R*,4a*S*,5*R*,8a*S*)-4a,5,8a-Trimethyl-2-methylenedecahydro-1-naphthalenyl)-3-methyl-1-penten-3-ol (1 and 14). Vinylmagnesium bromide (1 M in THF, 1.21 mL, 1.21 mmol) was added to a solution of **13** (32 mg, 0.122 mmol) in THF (2 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was dried and concentrated to leave a colorless oil, which was purified by chromatography (3% EtOAc/hexane) to give a mixture (1.2:1) of **1** and its epimer **14** (117 mg, 47% overall yield). **Compound 1:** ^{1}H NMR (500 MHz, COSY) δ 0.63 (s, Me-20), 0.73 (s, Me-19), 0.79 (d, J = 6.6 Hz, Me-18), 1.28 (s, Me-16), 1.29 (m, H-12), 1.34 (m, H-3), 1.35 (m, H-11), 1.36 (m, H-6), 1.42 (m, 3H), 1.48 (m, H-3, H-11), 1.53 (m, H-1), 1.59 (ddd, J = 14.5, 5, 2.5 Hz, H-6), 1.82 (ddd, J = 13,5, 13,5, 4,8 Hz, H-12); 2,05 (ddd, J = 14.5, 5, 2.5 Hz, H-7$_{eq}$), 2.18 (ddd, J = 14.5, 14.5, 5 Hz, H-7$_{ax}$), 2.33 (m, H-4), 2.56 (d, J = 11 Hz, H-9$_{ax}$), 4.50 (d, J = 1.5 Hz, H-17), 4.82 (d, J = 1.5 Hz, H-17), 5.05 (dd, J = 11, 1 Hz, H-15), 5.21 (dd, J = 17.5, 1.5 Hz, H-15), 5.92 (dd, J = 17.5, 11 Hz, H-14); ^{13}C NMR (100 MHz) δ 16.3 (C-18), 16.4 (C-19), 18.2 (C-11), 18.3 (C-20), 21.4 (C-2), 27.6 (C-16), 30.4 (C-4), 31.1 (C-3), 31.9 (C-1), 33.1 (C-7), 33.9 (C-6), 39.5 (C-5), 41.7 (C-12), 42.4 (C-10), 43.2 (C-9), 73.6 (C-13), 106.5 (C-17), 111.5 (C-15), 145.3 (C-14), 149.6 (C-8).

(*E*)-3-Methyl-5-[(1*R*,4a*S*,5*R*,8a*S*)-4a,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl]-pent-2-enoic Acid Methyl Ester (18). To a stirred slurry of NaH (64 mg, 1.58 mmol) in THF (3 mL) was added at 5 °C a solution of trimethyl phosphonoacetate in THF (2 mL). The reaction mixture was stirred for 2 h, after which a solution of **13** (52 mg, 0.198 mmol) in THF (3 mL) was added. The resulting mixture was heated at reflux for 10 h, allowed to reach room temperature; the reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc. The organic extract was washed with brine, dried, and concentrated to leave a colorless oil, which was purified by chromatography (1% EtOAc/hexane) to give 54 mg (85%) of a mixture (5:1) of **18** and its (*Z*)-isomer. **Compound 18:** ^{1}H NMR (500 MHz) δ 0.63 (s, 3H), 0.74 (s, 3H), 0.79 (d, J = 6 Hz, 3H), 1.20−1.60 (m, 8H), 1.54 (s, 3H), 1.55−1.60 (m, 2H), 1.90−2.15 (m, 3H), 2.20−2.40 (m, 2H), 2.62 (d, J = 11 Hz), 3.69 (s, 3H), 4.48 (d, J = 1 Hz), 4.86 (d, J = 1.5 Hz, 1H). 5.68 (s, 1H); ^{13}C NMR (75 MHz, DEPT) δ 16.3 (q), 16.4 (q), 18.3 (q), 19.1 (q), 21.4 (t), 22.4 (t), 30.4 (d), 31.2 (t), 32.0 (t), 33.1 (t), 33.9 (t), 39.5 (s), 40.1 (t), 42.3 (s), 42.4 (d), 50.8 (q), 106.3 (t), 114.7 (d), 149.2 (s), 161.2 (s), 167.2 (s). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.88; H, 10.94.

(*E*)-(1*R*,4a*S*,5*R*,8a*S*)-3-Methyl-5-(4a,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-pent-2-en-1-ol (19). A solution of a 5:1 mixture of esters **18** and its (*Z*)-isomer (35 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C, and DIBALH (1.5 M in toluene, 0.23 mL, 0.34 mmol) was added dropwise over 10 min. After being stirred at −78 °C for 45 min, the reaction was quenched by adding AcOH (5 M, 1 mL) in CH_2Cl_2 at −78 °C. The resulting mixture was allowed to reach room temperature, and 10% aqueous tartaric acid (2 mL) and H_2O (2 mL) were added. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated to leave a colorless oil, which was purified by chromatography (9:1 hexanes−EtOAc) to give **19** (22 mg, 69%; 85% based on **18**) and **20** (5 mg, 16%). **Compound 19:** $[\alpha]_D$ −22.3 (*c* 0.11, CH_2Cl_2); ^{1}H NMR (300 MHz) δ 0.63 (s, 3H), 0.73 (s, 3H), 0.79 (d, J = 6.9 Hz, 3H), 1.10−1.60 (m, 10H), 1.69 (s, 3H), 1.75−1.95 (m, 1H), 2.05 (m, 1H), 2.10−2.25 (m, 3H), 2.35 (m, 1H), 2.61 (d, J = 9.6 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 4.50 (s, 1H), 4.84 (s, 1H), 5.41 (tq, J = 6.9, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, DEPT) δ 16.3 (q), 16.4 (q), 16.5 (q), 18.3 (q), 21.4 (t), 22.6 (t), 30.4 (d), 31.2 (t), 31.9 (t), 33.1 (t), 33.9 (t), 38.7 (t), 39.5 (s), 42.2 (d), 42.4 (s), 59.5 (t), 106.2 (t), 122.9 (d), 140.7 (s), 149.5 (s); HRMS calcd for $C_{20}H_{34}O$ 290.2610, found 290.2614.

(1*R*,4a*S*,5*R*,8a*S*)-{3-Methyl-3-[2-(4a,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-ethyl]-(2*R*,3*R*)-oxiranyl}-methanol (21). D-(−)-Diethyl tartrate (13 μL, 0.062 mmol) and titanium(IV) isopropoxide (20 μL, 0.062 mmol) were added sequentially to a cooled (−20 °C) suspension of activated 4 Å molecular sieves and CH_2Cl_2 (0.5 mL). After the mixture was stirred at −20 °C for 10 min, *tert*-butyl hydroperoxide (23 μL, 5.5 M in decane, 0.128 mmol) was added and stirring was resumed for 45 min. Then, a mixture of **19** (18 mg, 0.062 mmol) in CH_2Cl_2 (0.5 mL) and activated 4 Å molecular sieves, cooled to −20 °C and previously stirred for 10 min, was added dropwise. After the mixture was stirred at −20 °C for 20 h, the reaction was quenched by addition of 10% aqueous tartaric acid (3 mL), resulting in the freezing of the aqueous layer. The cooling bath was removed and stirring was continued at room temperature. Hydrolysis of tartrates was effected by adding 2 mL of a 1 N aqueous NaOH solution and 2 mL of Et_2O. After 30 min of vigorous stirring at 0 °C, phase separation occurred. The organic phase was removed and combined with two extracts of the aqueous phase (CH_2Cl_2). The combined organic extracts were dried and filtered through Celite to give a clear, colorless solution. Concentration followed by purification of the oil by chromatography (85:15 hexanes−EtOAc) gave the epoxide **21** (10 mg, 53%): $[\alpha]_D$ −14.2 (*c* 0.06, $CHCl_3$); ^{1}H NMR (600 MHz, COSY) δ 0.64 (s, 3H, Me-20), 0.74 (s, 3H, Me-19), 0.79 (d, J = 7.2 Hz, Me-18), 1.31 (s, Me-16), 1.25 (m, 1H, H-12), 1.29 (m, 1H, H-3), 1.34 (m, 1H, H-11), 1.36 (m, 1H, H-6), 1.47 (m, 1H, H-3), 1.49 (m, 1H, H-11), 1.59 (dddd, J = 3, 4,2, 13,8 Hz, 1H, H-6), 1.88 (ddd, J = 4.2, 10.8, 15 Hz, H-12), 2.05 (dddd, J = 12.6, 6.6, 4.2, 2.4 Hz, 1H, H-7$_{ec}$), 2.17 (ddd, J = 4,2, 13,8 Hz, H-7$_{ax}$), 2.32 (m, 1H, H-4), 2.59 (d, J = 10.2 Hz, H-9$_{ax}$), 2.96 (dd, J = 6.6, 4.2 Hz H-14), 3.70 (dd, J = 11.5, 6.6 Hz, 1H, H-15), 3.85 (d, J = 11,5 Hz, 1H, H-15), 4.45 (brs, 1H, H-17), 4.83 (d, J = 1.2 Hz, 1H, H-17); ^{13}C NMR (100 MHz, HSQC) δ 16.3 (C-18), 16.4 (C-19), 16.9 (C-16), 18.3 (C-20), 19.2 (C-11), 21.4 (C-2), 31.1 (C-3), 30.4 (C-4), 31.9 (C-1), 33.9 (C-6), 33.0 (C-7), 37.6 (C-12), 39.5 (C-5), 42.3 (C-10), 42.7 (C-9), 61.5 (C-15), 62.5 (C-14), 62.7 (C-13), 106.6 (C-17), 149.4 (C-8); HRMS calcd for $C_{20}H_{35}O_2$ (MH^+) 307.2637, found 307.2644.

***ent*-Nakamurol A (1).** To a solution of epoxide **21** (10 mg, 0.033 mmol) in CH_2Cl_2 (0.5 mL) were added *p*-toluenesulfonyl chloride (7 mg, 0.036 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 5 h at room temperature. The crude was poured into hexanes (1.5

mL), and the resulting precipitate was removed by filtration. The filtrate was concentrated, diluted with Et_2O, and filtered again. The organic layer was dried and concentrated to give the corresponding tosylate (10 mg, 77%), which was used in the next step without purification. A solution of the above tosylate (9 mg, 0.025 mmol) in THF (0.5 mL) was added to a solution of sodium telluride at 50 °C prepared by reduction of elemental Te (6 mg, 0.047 mmol) with rongalite (14 mg, 0.075 mmol) and 1 M aqueous NaOH (80 μL, 0.075 mmol). After 5.30 h, the reaction was complete as indicated by TLC. The reaction mixture was exposed to air, and a stream of air was passed through it (0.5 h) to oxidize excess Te^{2-} to Te^0. The elemental tellurium was removed by filtration through Celite, after which the filter pad was washed with hexane. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and concentrated to leave an oil, which was purified by chromatography (8:2 hexanes−EtOAc) to give *ent*-nakamurol-A (**1**, 2.8 mg, 30%); $[\alpha]_D$ −36.3 (*c* 0.02, $CHCl_3$) [lit.[1] $[\alpha]_D$ +39.1 (*c* 1.6, $CHCl_3$)]. The ^1H NMR (500 MHz, COSY) and ^{13}C NMR (100 MHz, HSQC) data of **1** matched those reported in the literature for the natural product[1] as well as those of compound **1** obtained from **13** (see above): HRMS (FAB) calcd for $C_{20}H_{34}O$ 290.2610, found 290.2627.

Acknowledgment. This work was supported by the MCYT, Spain (project BQU2001-3551). Thanks are also due to the DURSI, Catalonia, for Grant 2001SGR-00083 and a fellowship for S.D.

Supporting Information Available: Experimental and/or NMR data for compounds **4**, **7**, **8**, **11**, **15**−**17**, and **20**, a table of ^{13}C NMR chemical shifts of all compounds reported, copies of ^1H and ^{13}C NMR spectra of all new compounds, as well as COSY and HSQC spectra when available. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034838R