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Total synthesis of (±)-nakamurol-A and its 13-epimer: tentative assignment of the C-13 relative configuration

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Abstract

A general approach to the structure of thelepogan-type diterpenoids has been developed and its application to the first total synthesis of (±)-nakamurol-A is described. The key steps involve: (i) a diastereoselective dimethylzinc addition to an endocyclic enone followed by enolate trapping; (ii) a Sakurai allylation of an exocyclic enone; and (iii) a Wacker chemoselective oxidation. The ^{1}H NMR data for the synthetic nakamurol-A and its C-13 epimer allow a tentative assignment of the relative configuration at C-13 of the natural product.

Keywords: terpenoids; stereocontrol; enones; allylation; sponges.

Nakamurol-A (**1**) is a novel terpenoid possessing a new carbon skeleton, recently isolated from the sponge *A. nakamurai*, collected at Okinawa, Japan.[1] An important characteristic of nakamurol-A is its stereostructure, with a contiguously arranged four-chiral center, C-4−C-5−C-10−C-9, for which the name thelepogane has been suggested.[2,3] The absolute configuration of nakamurol-A, as well as its relative configuration at C-13 are unknown so far.

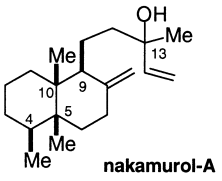

Figure 1.

We report here the first total synthesis of nakamurol-A (**1**) in its racemic form, and the elucidation of the relative configuration at C-13 of this diterpenoid. In planning the first synthetic approach to a thelepogane skeleton-bearing diterpenoid, we chose, as an advanced intermediate, the known enone **3**, in which two stereocenters have already been incorporated, and the generation

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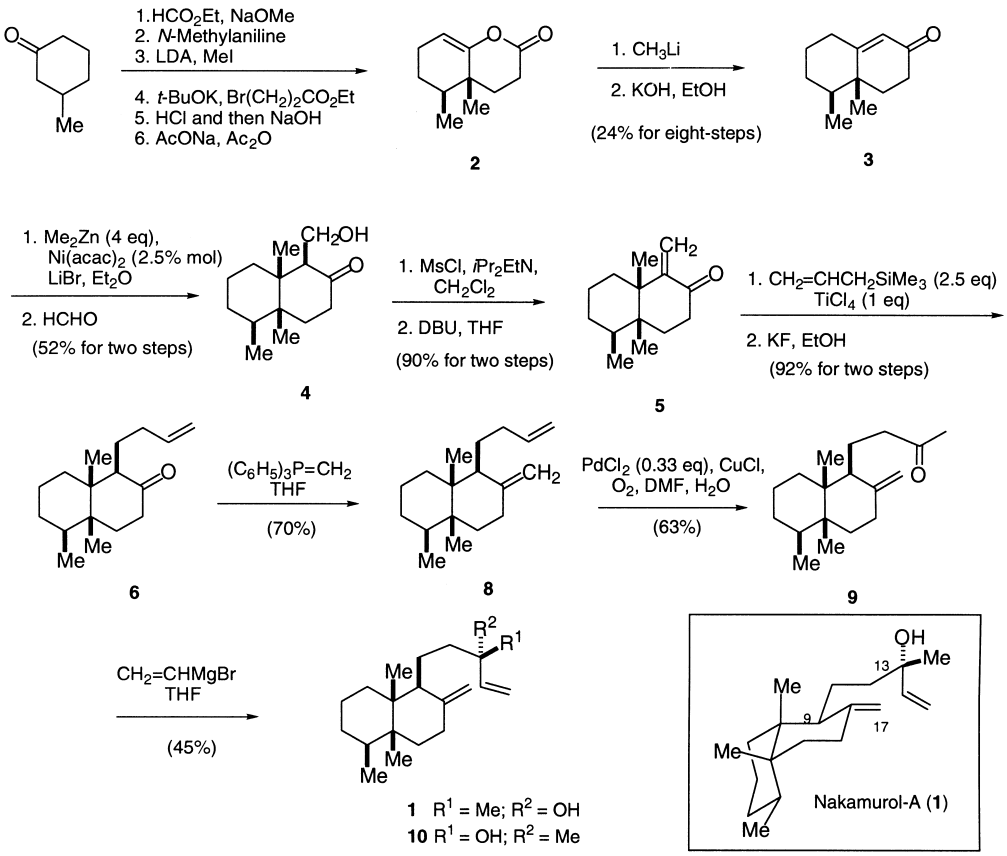
of the other two in the decaline ring would proceed from a conjugate addition and trapping of the enolate with an electrophile that, in turn, should allow the elaboration of the side chain at C-9 (Fig. 1).

The synthesis of (±)-**3** was carried out according to the Piers procedure,[4] following a slightly different protocol, depicted in Scheme 1. Starting from 3-methylcyclohexanone and obtaining as a key intermediate, the diastereomeric pure enol lactone **2**, the bicyclic enone **3** was prepared in an eight-step sequence and 24% overall yield.



Scheme 1.

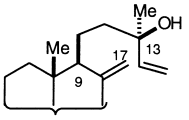
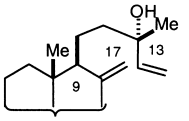
We then investigated the conjugate addition upon **3** (Me_2CuLi, Et_2O)[5] followed by enolate trapping (TMSCl), but this procedure to form the quaternary C-10 center was discarded since, in some runs, the tertiary alcohol coming from an initial 1,2-addition upon enone **3** was a significant by-product. In an attempt to circumvent this inconvenience, we proceeded to the $Ni(acac)_2$-catalyzed addition of dimethylzinc,[6] the 1,4-adduct now being the exclusive product. When the reaction mixture of **3** with dimethylzinc, in the aforementioned conditions, was treated at room temperature with gaseous formaldehyde,[7] keto alcohol **4** was obtained as the single diastereomer in 52% overall yield.[8] The stereochemistry of **4** was inferred from the chemical shift of C-2 (δ 21.4), which is a diagnostic value for the *cis*-fused decalone ring, and that of C-1 (δ 31.8), which is upfield by the hydroxymethyl substituent, equatorially located at C-9 with a 1,3-relationship with the H-1 equiv. (in the C-9 unsubstituted derivative, C-1 resonates at δ 35.9).

Mesylation of alcohol **4** followed by an elimination process induced by DBU gave α-methylene ketone **5**. The problem foreseen in the use of the α-methylene ketone **5** for this synthesis was the known susceptibility of such a system towards Diels–Alder type dimerization.[9] However, treatment of freshly prepared enone **5** with allyltrimethylsilane (2.5 equiv.) and $TiCl_4$ (1 equiv.), according to the usual protocol for a Sakurai reaction,[10] afforded keto alkene **6** in 94% yield as a 3:2 mixture of C-9 epimers enriched in the wanted isomer. Although adjusting the reaction conditions had little impact on this ratio,[11] it was possible to equilibrate the mixture to achieve the adequate stereochemistry. Thus, exposure of **6**, the mixture of epimers, to KF in refluxing ethanol led to a pure **6**, showing the butenyl side chain equatorially located.

The transformation of ketoalkene **6** to the target diterpenoid was accomplished as outlined. Wittig olefination of **6** afforded the bisalkene derivative **8**, which can be oxidized chemoselectively under the Wacker conditions ($PdCl_2$, CuCl, O_2) to afford the methyl ketone **9** in convenient yield. Grignard reaction of **9** using vinylmagnesium bromide gave a 1.2:1 mixture of nakamurol-A (**1**) and its C-13 epimer **10**.[12] ^{1}H NMR spectroscopic data for **1** were consistent with those reported for the natural product.[13]

The relative stereochemical assignment of C-13 for nakamurol-A and its epimer **10** was based on their ^{1}H NMR data, specifically the chemical shift of the vinyl protons at C-17 in the two isomers. These protons were observed at lower field and with a smaller Δδ between them in the natural compound, trends that have been consistently observed for related labdane diterpenoids with the 13*S* configuration, when compared with their epimers of 13*R* configuration (see Table 1). In this manner, with respect to a 9*S* configuration, the relative *S* configuration at C-13 for nakamurol-A is tentatively assigned by comparing the chemical shifts of both epimers **1** and **10** with those of other pairs of terpenoids and their epimers of known absolute configuration.

Table 1
^{1}H NMR chemical shifts (δ) for vinyl protons at C-17 for labdane-type diterpenoids and compounds **1** and **10**

Compounds with configuration 9*S*,13*R* 				Compounds with configuration 9*S*,13*S* 			
	$=CH_2$	Δδ	ref		$=CH_2$	Δδ	ref
compound **10**	4,45 / 4.80	0.35	*	nakamurol-A (**1**)	4.50 / 4.82	0.32	1, *
manool	4.46 / 4.80	0.34	14	13-epimanool	4.50 / 4.80	0.30	14
3α-hydroxymannol	4.49 / 4.82	0.33	15	3α-hydroxy-13-epimanool	4.53 / 4.83	0.30	12
3α-OTBS manool	4.46 / 4.79	0.33	12	3α-OTBS 13-epimanool	4.50 /4.80	0.30	12

* This work

In summary, the first total synthesis of (±)-nakamurol-A and its C-13 epimer has been completed in 16 steps and 2% overall yield from 3-methylcyclohexanone. In addition, this nakamurol-A synthesis serves to elucidate the relative stereochemistry of its C-13, a feature that was not assigned in the pioneering structure determination.[1] The synthesis of enantiopure nakamurol-A or its enantiomer is now under progress, starting from (–)-**3**, whose first enantiopure synthesis we have recently developed.[16]

Acknowledgements

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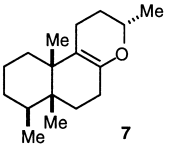
References

1. Shoji, N.; Umeyama, A.; Teranaka, M.; Arihara, S. *J. Nat. Prod.* **1996**, *59*, 448–450.
2. Thelepogine, isolated from the terrestrial grass *Thelepogan elegansas*, is the only diterpenoid alkaloid described so far with this backbone: Crow, W. D. *Aust. J. Chem.* **1962**, *15*, 159–161.
3. For a recent isolation of another thelepogan-type diterpenoid, see: Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M.; van Soest, R. W. M. C. *J. Nat. Prod.* **1998**, *61*, 1310–1312.
4. Piers, E.; Britton, R. W.; de Waal, W. *Can. J. Chem.* **1969**, *47*, 4307–4312.
5. For the addition of Me_2CuLi upon **3**, see: 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.
6. 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) Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
7. For the use of this trapping enolate agent on the synthesis of clerodane diterpenoids, see: Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, Y.; Monden, M.; Iio, H. *Tetrahedron* **1988**, *44*, 6607–6622.
8. All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C NMR, and elemental combustion analysis or high-resolution MS characteristics in accord with the proposed structures. ^{13}C NMR data (assignment aided by HSQC) for selected compounds: (**4**) 15.2 (C-18), 16.3 (C-19), 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), 216.1 (C-8). (**6**) 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-14), 139.0 (C-13), 213.6 (C-8). (**9**) 16.4 (C-18), 16.4 (C-19), 18.1 (C-11), 18.2 (C-20), 21.3 (C-2), 30.1 (C-14), 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).
9. This problem, previously recognized in the literature for related α-methylene ketones (Romann, E.; Frey, A. J.; Stadler, P. A.; Eschenmoser, A. *Helv. Chim. Acta.* **1957**, *40*, 1900–1917), was also observed for **6** whenever it was not quickly purified (bp 120°C/0.5 mmHg) and used in the next step.
10. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, 4041–4044.
11. When a slight excess of TiCl4 was used (1.5 equiv.), compound **6** was isolated (50% yield) together with the by-product **7** (30% yield).



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12. The same slight preference for the formation of the 13*S* epimer 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.
13. 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.
14. Barrero, A. F.; Sánchez, J. F.; Alvarez-Manzaneda, E. J.; Muñoz Dorado, M.; Haidour, A. *Phytochemistry* **1993**, *32*, 1261–1265.
15. 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.
16. Cuesta, X.; González, A.; Bonjoch, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3365–3370.