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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6493–6495

Synthetic studies on neomarinone: practical and efficient stereoselective synthesis of the side chain

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Received 29 May 2007; revised 5 July 2007; accepted 10 July 2007
Available online 14 July 2007

Abstract—A practical and efficient stereoselective synthesis of the side chain of neomarinone is reported. The synthesis was achieved in six steps (41% overall yield) from 2-methyl-2-cyclohexenone. The key step is a novel stereoselective 1,4-conjugate addition/enolate alkylation by an epoxide-opening reaction.

Neomarinone (**1**, Fig. 1) is a marine natural product isolated from the fermentation broth of actinomycetes strain #CNH-099 by Fenical et al. in 2000.[1] It belongs to a small group of prenylated naphthoquinones, including furaquinocin C (**2**)[2] and marinone (**3**),[3] with broad antibiotic and anticancer activities.[4] It displays moderate in vitro cytotoxicity ($IC_{50} = 8$ mg/mL) against HCT-116 colon carcinoma, a mean IC_{50} of 10 mM in assays with the NCI-60 panel of cancer cell lines, and moderate antibiotic activity. Structurally, neomarinone is a meroterpenoid (hybrid compounds of mixed polyketide-terpenoid origin)[5] that has a naphthoquinone unit linked to a ramified sesquiterpenoid side chain with four stereogenic centers, two of them being quaternary.

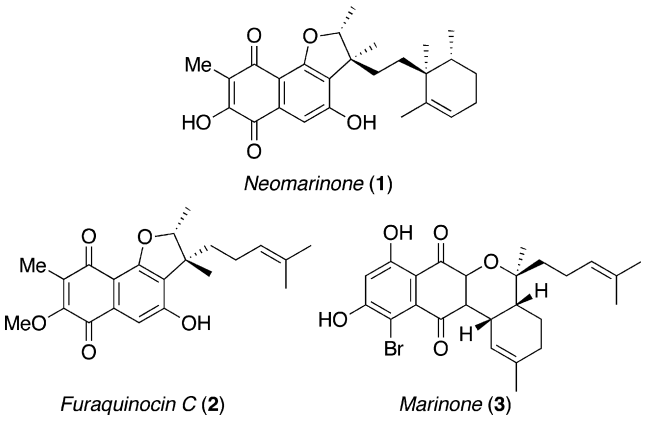

Figure 1. Neomarinone, furaquinocin C and marinone.

The structural elucidation of neomarinone has proved difficult due to the presence of five methyl groups in a small range of NMR chemical shifts. Indeed, in the initially proposed structure,[1] the stereochemistry of the methyl groups of the side chain was not determined. In 2003, biosynthetic studies on neomarinone by Moore et al. led to its structural revision, with correction of the structure of the side chain (Fig. 1).[6] The stereochemistry of the methyl groups in the cyclohexenyl unit of neomarinone was assigned cis, based on chemical correlation with the natural products ageline A[7] and subersine,[8] which have the same cyclohexenyl unit with cis and trans stereochemistry, respectively. The relative stereochemistry of the methyl groups of the furan ring was assigned by chemical comparison with (−)-furaquinocin C and (+)-3-epifuraquinocin C.[9] However, the configuration of the methyl groups of the cyclohexenyl ring relative to the methyl groups of the furyl residue could not be unequivocally determined.

The retrosynthetic analysis for neomarinone is depicted in Scheme 1. In this approach, the naphthofuranic skeleton would be obtained by a regioselective Diels–Alder reaction between a bromoquinone (**4**, Scheme 1) and a 1,3-bis(trimethylsilyloxy)-1,3-diene (**5**) containing the side chain; the quaternary stereocenter at the furyl ring would then be formed by diastereoselective conjugate addition of an organometallic reagent derived from

Keywords: Natural product synthesis; 1,4-Addition reactions; Enolate alkylation reactions; Stereoselective synthesis.
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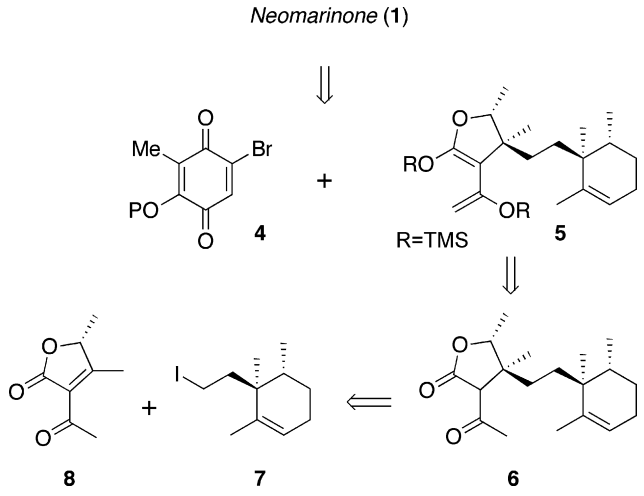
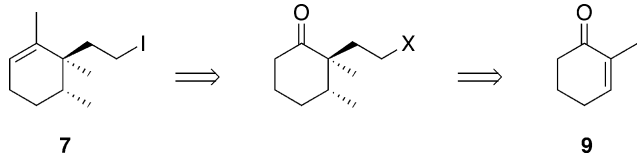
doi:10.1016/j.tetlet.2007.07.064



Scheme 1. Retrosynthetic analysis for neomarinone.

iodide **7** to the α,β-unsaturated lactone **8**. In this Letter, we report a practical and efficient stereoselective synthesis of iodide **7**.

For stereoselective synthesis of iodide **7**,[10] we devised an expedient synthetic procedure from 2-methyl-2-cyclohexenone (**9**), using as key step for generating the chiral centers, a stereoselective tandem conjugate addition/enolate alkylation reaction with a C_2 electrophile (Scheme 2). The 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl systems followed by enolate trapping with electrophiles constitutes an elegant methodology for the preparation of functionalized cycloketones and derivatives.[11] Although in these tandem reactions alkyl halides and aldehydes are the most widely used electrophiles, we decided to explore the utility of an epoxide such as ethylene oxide.

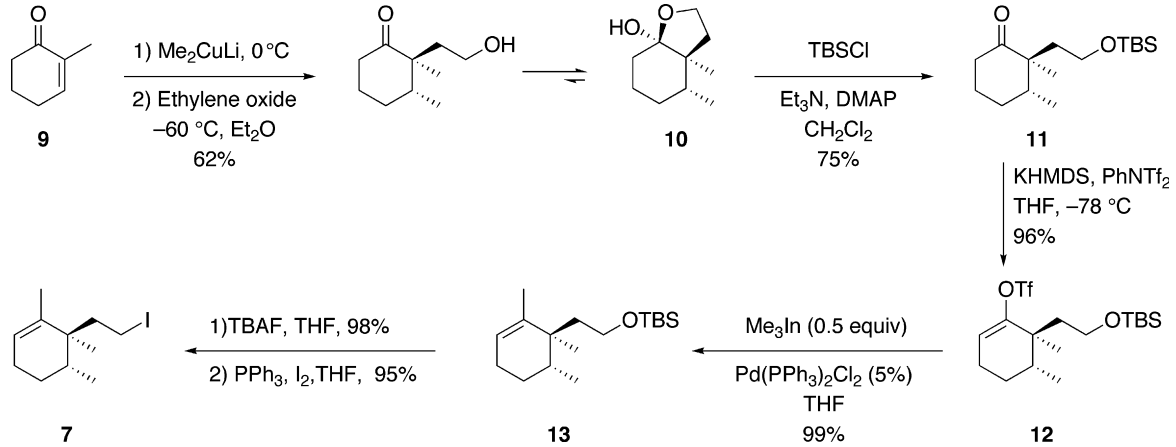


Scheme 2. Retrosynthetic analysis for iodide **7**.

During our investigation, we found that the reaction of 2-methyl-2-cyclohexenone (**9**)[12] with lithium dimethyl cuprate, followed by addition of ethylene oxide at low temperature, afforded hemiketal **10** in 62% yield as a single diastereoisomer as shown by ^{1}H NMR (Scheme 3).[13] The formation of **10** can be reasonably explained by the cyclization of the intermediate γ-hydroxyketone. The relative stereochemistry of the methyl groups in **10** was determined to be cis by NOESY experiments, demonstrating that the enolate alkylation takes place *anti* to the methyl group at β-position. This reaction is, to the best of our knowledge, the first example of a tandem conjugate addition–enolate alkylation reaction using an epoxide as the electrophile.

In the next step, hemiketal **10**, in equilibrium with the corresponding γ-hydroxyketone compound, was transformed into silylether **11** by treatment with TBSCl (1.5 equiv) and Et_3N (1.2 equiv) in the presence of catalytic amounts of DMAP (15%) in CH_2Cl_2 (75% yield). For transformation of cyclohexanone **11** into 1-methylcyclohexene **13**, we considered the application of our recently developed palladium-catalyzed cross-coupling reaction of indium organometallics with alkenyl electrophiles.[14] Therefore, ketone **11** was transformed into a vinyl triflate by treatment with KHMDS followed by addition of $PhNTf_2$, affording **12** in high yield (96%).[15] The palladium-catalyzed cross-coupling reaction of **12** with trimethylindium (0.5 equiv) in the presence of catalytic amounts of $Pd(PPh_3)_2Cl_2$ (5 mol %) afforded the coupling product **13** in quantitative yield. Finally, cleavage of silylether **13** with tetrabutylammonium fluoride (3 equiv) at room temperature for 2 h gave the corresponding alcohol that, without further purification, was converted to the desired iodide **7**[16] by treatment with PPh_3 and I_2 in 98% yield.

In summary, iodide **7**, containing the cyclohexenyl unit of the side chain of neomarinone, has been synthesized in six steps from 2-methyl-2-cyclohexenone (41% overall yield), a synthetic procedure that allows the preparation of iodide **7** in a multigram scale. The key step of the synthesis is a novel stereoselective tandem 1,4-conjugate addition/enolate alkylation by an epoxide-opening reac-



Scheme 3. Synthesis of iodide **7**.

tion. The synthesis of racemic iodide **7** should allow the total synthesis of neomarinone and its diastereoisomers, and should provide useful data for establishing the relative stereochemistry of the cis methyl groups of the cyclohexane unit with respect to the cis methyl groups of the furan ring, and the absolute configuration of neomarinone.

Acknowledgments

This research was supported by the Xunta de Galicia (Spain, PGIDIT05BTF10301PR) and Ministerio de Educación y Ciencia (Spain, CTQ2006-06166). R.M.S. thanks the Ministerio de Educación y Ciencia for an FPU fellowship and M.M.M. thanks Xunta de Galicia for a research contract sponsored by the Isidro Parga Pondal program.

References and notes

1. Hardt, I. H.; Jensen, P. R.; Fenical, W. *Tetrahedron Lett.* **2000**, *41*, 2073–2076.
2. (a) Ishibashi, M.; Funayama, S.; Anraku, Y.; Komiyama, K.; Omura, S. *J. Antibiot.* **1991**, *44*, 390–395; (b) Funayama, S.; Ishibashi, M.; Komiyama, K.; Omura, S. *J. Org. Chem.* **1990**, *55*, 1132–1133.
3. Pathirana, C.; Jensen, P. R.; Fenical, W. *Tetrahedron Lett.* **1992**, *33*, 7663–7666.
4. Kuzuyama, T.; Seto, H. *Nat. Prod. Rep.* **2003**, *20*, 171–183.
5. Simpson, T. J. *Top. Curr. Chem.* **1998**, *195*, 1–48.
6. Kalaitzis, J. A.; Hamano, Y.; Nilsen, G.; Moore, B. S. *Org. Lett.* **2003**, *5*, 4449–4452.
7. Capon, R. J.; Faulkner, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 1819–1822.
8. Carroll, J.; Jonsson, E. N.; Ebel, R.; Hartman, M. S.; Holman, T. R.; Crews, P. *J. Org. Chem.* **2001**, *66*, 6847–6851.
9. Smith, A. B.; Pérez Sestelo, J.; Dormer, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 10755–10756.
10. Iodide **7** had been prepared previously, although by a long and impractical synthetic sequence: Asao, K.; Iio, H.; Tokoroyama, T. *Tetrahedron Lett.* **1989**, *30*, 6401–6404.
11. For an exhaustive review of this type of reaction, see: (a) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225–653; For key references, see: (b) Rathgeb, X.; March, S.; Alexakis, A. *J. Org. Chem.* **2006**, *71*, 5737–5742; (c) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141–5144; (d) Boeckman, R. K., Jr. *J. Org. Chem.* **1973**, *38*, 4450–4452.
12. Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth. Coll.* **1963**, *4*, 162–166.
13. *Experimental procedure*: To a cooled solution of methyl cuprate in Et_2O (10 mL, 1 M) at 0 °C, a solution of 2-methyl-2-cyclohexenone (**9**, 1 g, 9.08 mmol) in Et_2O (9 mL) was added via cannula. After 1 h stirring, the reaction mixture was cooled at −60 °C and a freshly prepared cooled solution (0 °C) of ethylene oxide in Et_2O was added via cannula. The reaction mixture was slowly warmed to room temperature in a 12 h period, quenched by addition of NH_4OH (30%):NH_4Cl (satd. sol.) (2:1, 20 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layer was washed with saturated aqueous NH_4Cl solution (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by column chromatography (15% EtOAc/hexanes) giving 960 mg of hemiketal **10** as a white solid [62%, $R_f = 0.25$ (30% EtOAc/hexanes)]. Mp 81–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, $J = 6.6$ Hz, 3H), 0.97 (s, 3H), 1.07–1.23 (m, 1H), 1.38–1.66 (m, 4H), 1.84–1.89 (m, 1H), 1.90 (s, 3H), 1.93–2.00 (m, 1H), 3.89 (dd, $J = 16.7$, 8.5 Hz, 1H), 3.99 (dt, $J = 9.3$ 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8 (CH_3), 16.7 (CH_3), 22.6 (CH_2), 29.8 (CH_2), 33.0 (CH_2), 34.6 (CH_2), 35.5 (CH), 47.5 (C), 64.1 (CH_2), 105.8 (C); IR (NaCl) 3401, 2959–2934, 915 cm^{-1}; MS (EI, 70 eV) *m*/*z* 171 (M^++H, 3), 170 (M^+, 8), 153 (M^+−OH, 56), 126 ($M^+-C_2H_4O$, 33), 83 (100); HRMS (FAB) Calcd for $C_{10}H_{19}O_2$ 171.1385 (M^++H); found, 171.1379.
14. (a) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269; (b) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160.
15. (a) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47–54; (b) Ritter, K. *Synthesis* **1993**, 735–762.
16. *Spectroscopic data for iodide* **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 0.89 (d, $J = 6.9$ Hz, 3H), 1.37–1.51 (m, 2H), 1.63 (br s, 3H), 1.91–1.96 (m, 2H), 2.09 (m, 2H), 2.88 (dt, $J = 9.7$, 7.3 Hz, 1H), 3.13 (dt, $J = 9.3$, 7.3 Hz, 1H), 5.48 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.3 (CH_2), 15.9 (CH_3), 19.2 (CH), 20.5 (CH_3), 25.4 (CH_2), 26.7 (CH_2), 33.1 (CH_3), 41.9 (CH_2), 43.5 (C), 125.2 (CH), 138.1 (C); IR (NaCl) 3019, 2963–2835, 1464, 1160, 562 cm^{-1}; MS (EI, 70 eV) *m*/*z* 278 (M^+, 2), 123 ($M^+-C_2H_4I$, 100); HRMS (EI) Calcd for $C_{11}H_{19}I$, 278.0532 (M^+); found, 278.0521.