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Synthetic approaches to neorogiolanes: enantiospecific synthesis of 12-methoxyneorogiola-1,3,5,7(17),8-pentaene

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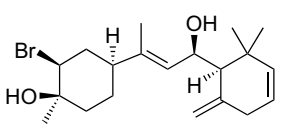
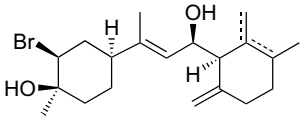
Abstract—Enantiospecific synthesis of 12-methoxyneorogiola-1,3,5,7(17),8-pentaene, containing the complete carbon framework of the natural diquinane diterpenes neorogioldiols, starting from (*S*)-campholenaldehyde is described.

1. Introduction

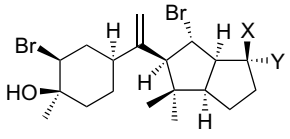
Species of the red alga genus *Laurencia* (Huds.) Lamoroux is a source of a variety of structurally unusual secondary metabolites and have been the subject of intensive research.[1] The red seaweed *Laurencia microcladia* Kutzning, which has colonized a short tract of the Tuscany coast called Il Rogiolo, is a prolific source of a variety of secondary metabolites, such as acetogenins, obtusane diterpenes rogioldiols A–C **1** and **2**. In 2000, Guella and Pietra reported the isolation and structural elucidation of a diterpene neorogioldiol **3a** containing a new diquinane carbon framework, 2,2,6-trimethyl-3-[1-(4-methylcyclohexyl)vinyl]bicyclo[3.3.0]octane named neorogiolane **4**, from this sea weed.[2] Subsequently, Roussis et al. reported the isolation of **3a** along with its C-11 epimer **3b** and prevozols B–E **5** and **6** from *Laurencia obtuse*, collected from the coastal rocks of Preveza in the Ionean Sea[3] as part of their studies on the isolation of biologically active compounds from marine organism of the Greek seas. All these compounds **3**, **5** and **6** were found to exhibit potent cytotoxic activity against five human cell lines. PC3 and HeLa cells were found to be more sensitive to compound **3b** among these compounds. The presence of a diquinane moiety in neorogioldiols **3a** and **3b** coupled with their potent cytotoxic reactivity against human cell lines make them interesting synthetic targets. In continuation of our interest in the synthesis of enantiopure natural products and their analogues employing chiral pool



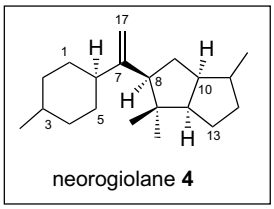
rogioldiols A **1**



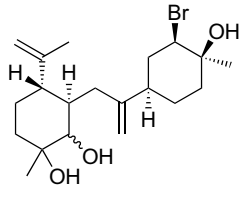
rogioldiols B and C **2**



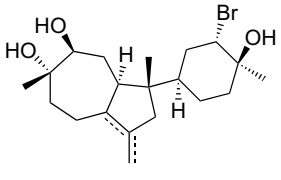
X=Me, Y=OH; neorogioldiol A **3a**
X=OH, Y=Me neorogioldiol B **3b**



neorogiolane **4**



prevezols B and C **5**



prevezols D and E **6**

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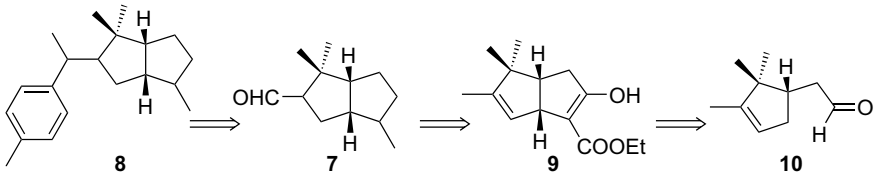
approach,[4] we have initiated the synthesis of neorogiolanes **4** in enantiopure form.[5] Herein, we report an enantiospecific synthesis of a neorogiolane, containing the complete carbon framework **4** of neorogioldiols **3**.

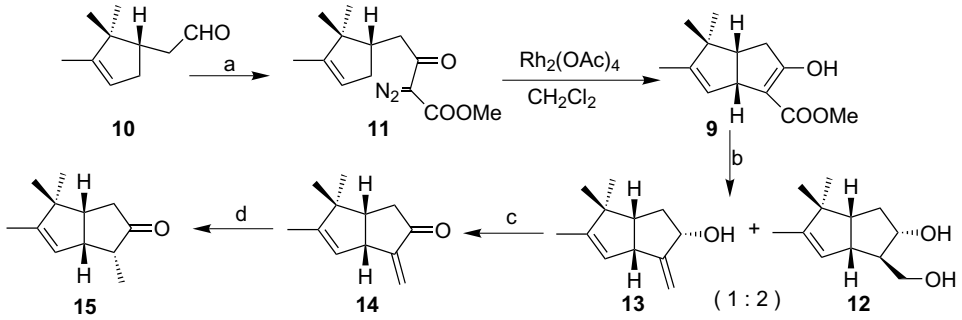
2. Results and discussion

It was contemplated that coupling an aryl group to diquinane aldehyde **7** would lead to an aromatic analogue **8** of neorogiolane **4** (Scheme 1). Aldehyde **7** could be obtained from bicyclic ketoester **9**, whose synthesis from campholenaldehyde **10** has already been developed in our laboratory.[6]

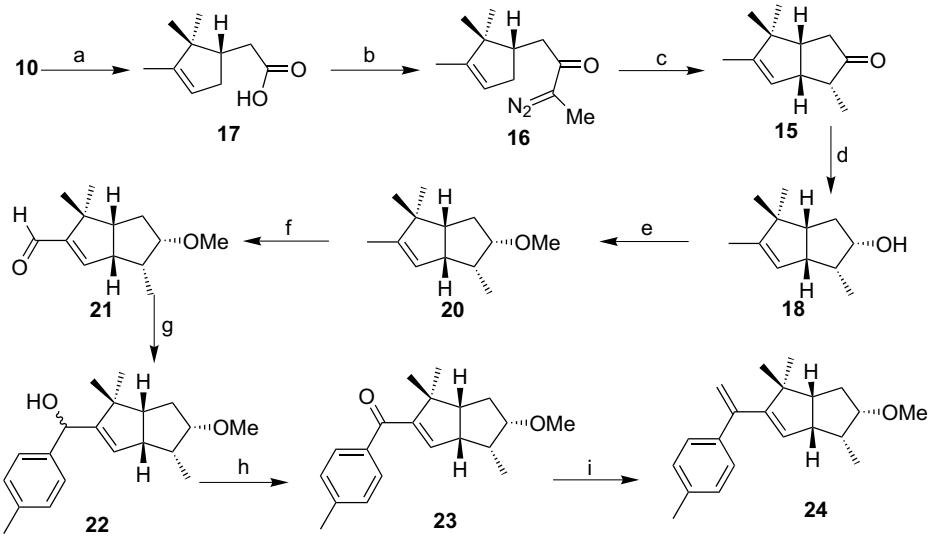
The synthetic sequence is depicted in Scheme 2. To begin with, campholenaldehyde **10** was converted into diquinane keto ester **9**, via an intramolecular rhodium carbenoid CH insertion[7] of diazoketone **11**. For the conversion of the ester group into a methyl group, the reduction of keto ester **9** into diol **12** was first attempted. Interestingly, the reaction of the ketoester **9** with lithium aluminium hydride



Scheme 1.



Scheme 2. Reagents and conditions: (a) Ref. 6; (b) LAH, Et_2O, 0 °C, 1 h, 84%; (c) PCC, silica gel, CH_2Cl_2, rt, 2 h, 79%; (d) Li, liq. NH_3, *t*-BuOH, THF, 10 min, 81%.



Scheme 3. Reagents and conditions: (a) Jones reagent (1.25 M), $Me_2C{=}O$, 0 °C, 0.5 h, 94%; (b) (i) $(COCl)_2$, C_6H_6, rt, 2 h; (ii) CH_3CHN_2, Et_2O, 0 °C→rt, 1 h, 70%; (c) $Rh_2(OAc)_4{\cdot}2H_2O$, CH_2Cl_2, reflux, 3 h, 61%; (d) $NaBH_4$, MeOH, 0 °C, 10 min, 93%; (e) NaH, THF, TBAI, MeI, 89%; (f) SeO_2, AcOH, reflux, 1.5 h, 63%; (g) Li, 4-bromotoluene, THF,))), 1 h, 86%; (h) PDC, CH_2Cl_2, rt, 3 h, 80%; (i) MeMgI, Et_2O, 0 °C→rt, 0.75 h; aq NH_4Cl, 80%.

(LAH) in ether furnished a 1:2 mixture of allyl alcohol **13** and diol **12**, which was separated by column chromatography on silica gel.[8] Oxidation of allyl alcohol **13** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished enone **14**, which on reduction with lithium in liquid ammonia furnished diquinane **15** in a highly stereoselective manner (>95% by NMR).

In an alternative strategy it was contemplated that diquinane **15** could be obtained directly by an intramolecular rhodium carbenoid insertion reaction of diazoketone **16** (Scheme 3). Thus, the reaction of acid **17** with oxalyl chloride, followed by treatment of the resulting acid chloride with an excess of diazoethane ether solution furnished diazoketone **16**. Refluxing a methylene chloride solution of diazoketone **16** with a catalytic amount of rhodium acetate[7] furnished diquinane **15**, in 61% yield, in a highly stereoselective manner (>95% by ^{1}H and ^{13}C NMR), which was found to be identical to that obtained from ketoester **9**. For further elaboration of diquinane **15** into a neorogiolane, it was contemplated to protect the ketone moiety. Consequently, reduction of ketone **15** with sodium borohydride in methanol furnished alcohol **18** in a highly stereoselective manner (>95%) via the approach of the hydride from the *exo* face of the molecule. In order to confirm the stereochemistry of the methyl and hydroxy groups in **18**, it was converted into the corresponding 3,5-dinitrobenzoate **19**. Single crystal X-ray diffraction analysis of dinitrobenzoate **19**, Figure 1, unambiguously established the stereostructure of diquinane **18**. The hydroxy group in diquinane **18** was protected as its methyl ether **20** by treating with sodium hydride and methyl iodide in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) in THF.

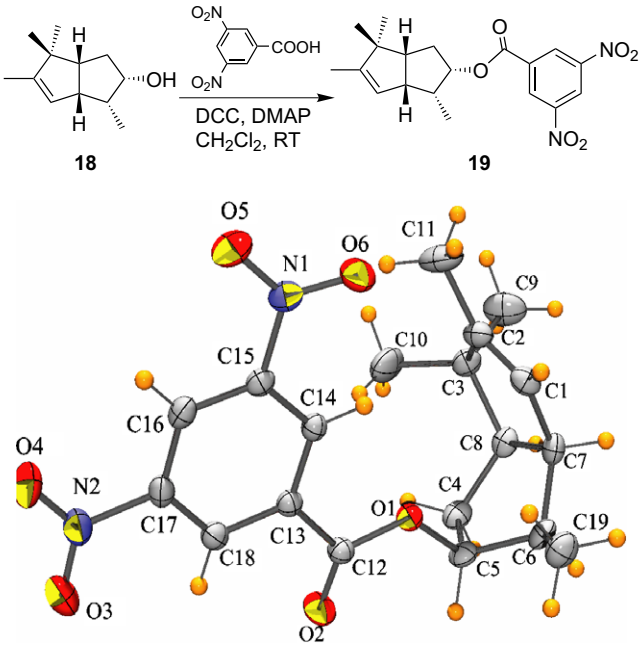


Figure 1. ORTEP diagram of ester **19**.

After successfully constructing the diquinane part of neorogiolane **4**, oxidation of the olefinic methyl group was explored. Thus, the reaction of diquinane **20** with 3 equiv of selenium dioxide in refluxing acetic acid furnished the aldehyde **21** in 63% yield, the structure of which was established from its spectral data. Coupling of aldehyde **21** with 4-bromotoluene in THF under sonochemically accelerated Barbier conditions resulted in the formation of secondary alcohol **22** in 86% yield, which upon oxidation with PDC in methylene chloride furnished enone **23** in 80% yield. Finally, the reaction of enone **23** with methylmagnesium iodide in ether, followed by in situ dehydration of the resulting tertiary alcohol furnished 12-methoxyneorogiola-1,3,5,7(17),8-pentaene **24** containing the complete carbon framework **4** of neorogioldiols, in 80% yield, whose structure was established from its spectral data.

3. Conclusion

In conclusion, we have developed an enantiospecific methodology for the synthesis of an aromatic neorogiolane **24** containing the complete carbon framework of neorogioldiols starting from campholenaldehyde, which is accessible from the abundantly available monoterpene α-pinene. We are currently investigating the extension of the methodology for the synthesis of non-aromatic analogues and the natural neorogioldiols.

4. Experimental

Yields refer to isolated and chromatographically pure compounds. All compounds exhibited spectral data (IR, ^{1}H and ^{13}C NMR and HRMS) consistent with their structures. Selected spectral data for the diquinane **15**: $[\alpha]_D^{22} = -41.5$ (*c* 5.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1740; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.09 (1H, br s, H-6), 3.40–3.30 (1H, m, H-5), 2.53–2.00 (4H, m), 1.56 (3H, s, olefinic CH_3), 1.03 (3H, d, *J* 7.2 Hz, *sec*-CH_3), 1.00 (3H, s) and 0.93 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 218.6 (C, C=O), 148.5 (C, C-7), 121.3 (CH, C-6), 48.6 (2C, CH), 47.8 (C, C-8), 46.8 (CH), 38.3 (CH_2, C-2), 26.4 (CH_3), 21.8 (CH_3), 12.8 (CH_3), 11.3 (CH_3); HRMS: *m*/*z* calcd for $C_{12}H_{18}ONa$ (M+Na): 201.1255; found: 201.1248. For dinitrobenzoate **19**: mp: 91–92 °C; $[\alpha]_D^{23} = -54.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1728, 1628, 1548; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 9.19 (1H, t, *J* 2.1 Hz,) and 9.05 (2H, d, *J* 2.1 Hz) [ArH], 5.50–5.30 (2H, m, H-3 and 6), 3.30–3.20 (1H, m, H-5), 2.51 (1H, q, *J* 7.5 Hz), 2.40–2.25 (1H, m), 2.17–1.00 (2H, m), 1.68 (3H, s, olefinic CH_3). 1.07 (3H, d, *J* 7.2 Hz, *sec*-CH_3), 1.06 (3H, s) and 0.95 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 161.9 (C, C=O), 148.8 (2C), 147.2 (C, C-7), 134.6 (C), 129.2 (2C, CH), 123.1 (CH), 122.1 (CH, C-6), 82.0 (CH, C-3), 51.9 (CH), 51.8 (CH), 48.2 (C, C-8), 41.7 (CH, C-5), 34.1 (CH_2,C-2), 29.8 (CH_3), 23.0 (CH_3), 12.6 (CH_3), 11.6 (CH_3); HRMS: *m*/*z* calcd for $C_{19}H_{22}N_2O_6Na$ (M+Na): 397.1376; found: 397.1361. Crystal data for dinitrobenzoate **19**: X-ray data were collected at 273 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct

methods (SIR 92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Mol. For. $C_{19}H_{22}N_2O_6$; MW = 374.39; light yellow crystal; crystal system: triclinic; space group $P\bar{1}$; cell parameters, $a = 6.930(5)$ Å, $b = 11.193(7)$ Å, $c = 13.047(9)$ Å; α 74.774(11), β 75.890(11), γ 83.013(11), $V = 945.3(11)$ Å^3, $Z = 2$, $D_c = 1.315$ g cm^{-3}, $F(000) = 396$, $\mu = 0.099$ mm^{-1}. Total number of l.s. parameters = 248, $R_1 = 0.0505$ for 2754 $F_0 > 2\sigma(F_0)$ and 0.0652 for all 3500 data. $wR_2 = 0.1202$, GOF = 1.051, restrained GOF = 1.051 for all data. An ORTEP diagram is depicted in Figure 1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 634856). For methyl ether **20**: $[\alpha]_D^{23} = -23.9$ (*c* 16.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1514, 1109; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.10 (1H, br s, H-2), 3.53 (1H, ddd, *J* 12.6, 8.1 and 5.4 Hz, H-7), 3.26 (3H, s, OCH_3), 3.06 (1H, tt, *J* 7.8 and 2.4 Hz, H-1), 2.32–2.12 (2H, m), 1.70 (1H, ddd, *J* 12.6, 8.1 and 5.4 Hz), 1.58 (3H, s, olefinic CH_3), 1.57–1.44 (1H, m), 0.99 (3H, s) and 0.95 (3H, s) [2 × *tert*-CH_3], 0.78 (3H, d, *J* 7.2 Hz, *sec*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 146.1 (C, C-3), 123.5 (CH, C-2), 84.8 (CH, C-7), 57.1 (CH_3, OCH_3), 50.6 (CH), 49.1 (CH), 46.9 (C, C-4), 36.9 (CH), 30.9 (CH_2, C-6), 29.4 (CH_3), 22.2 (CH_3), 12.6 (CH_3), 11.0 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{22}ONa$ (M+Na): 217.1204; found: 217.1203. For ketone **23**: $[\alpha]_D^{25} = -32.4$ (*c* 5.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1643, 1605, 871, 837, 755; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.76 and 7.23 (4H, 2 × d, *J* 8.1 Hz, ArH), 6.20 (1H, d, *J* 2.1 Hz, H-2), 3.60 (1H, q, *J* 5.4 Hz, H-7), 3.34 (3H, s, OCH_3), 3.40–3.20 (1H, td, *J* 8.1 and 2.1 Hz, H-1), 2.44 (3H, s, $ArCH_3$), 2.50–2.20 (2H, m), 2.02 (1H, ddd, *J* 13.8, 6.0 and 3.9 Hz), 1.79 (1H, ddd, *J* 13.8, 9.9 and 5.1 Hz), 1.40 (3H, s) and 1.25 (3H, s) [2 × *tert*-CH_3], 1.05 (3H, d, *J* 9.0 Hz, *sec*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 194.4 (C, C=O), 148.4 (C), 144.5 (CH, C-2), 142.1 (C), 137.6 (C), 129.8 (2C, CH), 128.7 (2C, CH), 84.8 (CH, C-7), 56.7 (CH_3, OCH_3), 53.1 (CH, C-5), 52.4 (CH, C-8), 48.7 (C, C-4), 41.2 (CH, C-1), 31.6 (CH_2, C-6), 30.8 (CH_3), 22.1 (CH_3), 21.7 (CH_3), 11.6 (CH_3); HRMS: *m*/*z* calcd for $C_{20}H_{27}O_2$ (M+H): 299.2011; found: 299.2005. For neorogiolapentaene **24**: $[\alpha]_D^{24} = -26.5$ (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1115, 813; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.24 and 7.04 (4H, 2 × d, *J* 8.1 Hz, ArH), 5.42 (1H, d, *J* 2.1 Hz, H-2), 5.19 and 5.03 (2H, 2 × d, *J* 2.4 Hz, C=CH_2), 3.54 (1H, q, *J* 6.0 Hz), 3.30 (3H, s, OCH_3), 3.23–3.13 (1H, td, *J* 8.1 and 2.1 Hz), 2.33 (3H, s, $ArCH_3$), 2.32–2.20 (2H, m), 1.77–1.68 (2H, m), 1.09 (3H, s) and 0.90 (3H, s) [2 × *tert*-CH_3], 0.94 (3H, d, *J* 7.2 Hz, *sec*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 150.2 (C), 146.2 (C), 139.7 (C), 136.7 (C), 130.4 (CH), 128.6 (2C, CH), 127.5 (2C, CH), 113.3 (CH_2, C=CH_2), 84.8 (CH), 57.1 (CH_3, OCH_3), 52.6 (CH), 50.0 (CH), 48.3 (C), 38.5 (CH), 31.4 (CH_2), 30.9 (CH_3), 23.1 (CH_3), 21.3 (CH_3), 11.5 (CH_3); HRMS: *m*/*z* calcd for $C_{21}H_{28}ONa$ (M+Na): 319.2038; found: 319.2039.

Acknowledgements

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5. To the best of our knowledge there is no report in the literature on the synthesis of any neorogiolane either in racemic or enantiopure form.
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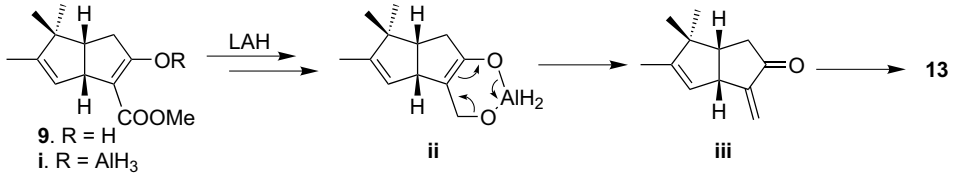
8. The stereochemistry of diol **12** was assigned tentatively on the assumption of the preferred stereochemistry of starting keto ester **9**. The stereochemistry of allyl alcohol **13** was assigned on the basis of the preferred approach of the reagent from the *exo* face of enone **iii**. The formation of allyl alcohol **13** from ketoester **9** could be rationalised via the intermediate aluminium species **ii** as depicted below, followed by further reduction of the resultant enone **iii**.



9. R = H
i. R = AlH_3
ii
iii