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Synthesis of (+)-makassaric acid, a protein kinase MK2 inhibitor

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ABSTRACT

Description of the first synthesis of (+)-makassaric acid, an important kinase MK2 inhibitor. The key step was a Barton/McCombie radical deoxygenation.

1. Introduction

(−)-Subersic acid, **1**, was isolated recently from the Papua New Guinean sponge *Suberea* sp. and exhibited biological activity as an inhibitor of human 15-lipooxygenase.[1]

The stereochemistry of this sponge-derived was established as (5*R*,10*R*), **1**, by total synthesis, by Mori et al.[2] The main strategy of this synthesis is the coupling of a sulfone derivative of a decalin obtained from (*S*)-3-hydroxy-2,2-dimethylcyclohexanone and an aromatic prenylated derivative obtained from *p*-hydroxybenzoic acid. Another total synthesis of (−)-subersic acid was carried out by Stille coupling, between a stannane aromatic derivative of *p*-hydroxybenzoic acid and the allyl trifluoroacetate derivative of the diterpene unit obtained from (8a*R*)-bicyclofarnesol by Akita et al.[3] In addition, the synthesis of (+)-subersic acid, **2**, was achieved by coupling of an aromatic lithium derivative of *p*-hydroxybenzoic acid and an diterpene allyl bromide obtained from the natural product sclareol by us.[4] Later, in 2004, Andersen et al.[5] isolated (+)-subersic acid, **2** and (+)-makassaric acid, **3**, from the marine sponge *Acanthodendrilla* sp. The two meroterpenoids **2** and **3** were inhibitors of the protein kinase MK2 (Fig. 1).

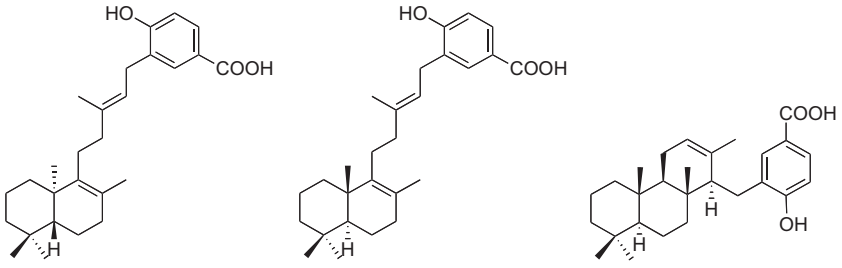

Figure 1. Some meroterpenoids with biological activity.

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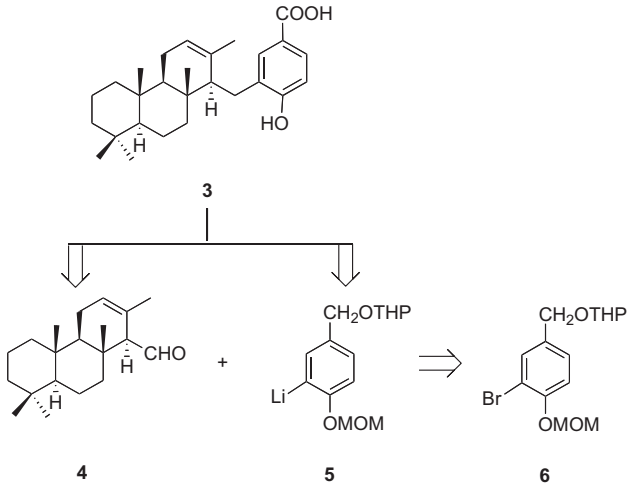
The biological activities of all of these meroterpenes are related to the control of antiinflammatory processes. Inflammation represents a host defence response to traumatisms, infections, ischemia, toxics or autoimmune injuries.[6]

Inflammatory stimuli activate many intracellular signalling pathways. Among them, the p38 MAPK is considered to be a central regulator of inflammation.[7] Subsequently, efforts have been made to search for MK2 inhibitors from natural products, and we, particularly, became interested in synthesizing (+)-makassaric acid, **3**.

2. Results and discussion

Scheme 1 shows our synthetic plan for (+)-makassaric acid: the target molecule **3** was to be constructed by the coupling of the diterpenic moiety, aldehyde **4** and an aromatic lithium derivative **5**, appropriately protected. The last compound can be provided by lithiation of the bromoderivative **6**.



Scheme 1. Retrosynthetic analysis of (+)-makassaric acid.

Aldehyde **4** was a key intermediate in our previous synthesis of luffolide[8] and it was obtained from methyl isoanticopalate, which has been obtained from (−)-sclareol[9] (Scheme 2). Moreover, this compound has been used in the synthesis of several biologically active spongianes.[10]

After NMR studies and mainly based on ROESY experiments, NOEs between H-15 and H-7β, H-14 and Me-17, we concluded that the configuration for **7** at C-15 is (*S*) Scheme 3.

With alcohol **7** in our hands, the next requirement for the synthesis of (+)-makassaric acid was the deoxygenation at C-15.

Our first attempt was to carry out the deoxygenation through the Huang-Millon procedure[11] (Scheme 4). Oxidation of **7** with TPAP under standard conditions[12] led to ketone **8** with excellent yield. However, treatment of ketone **8** with KOH/H_2NNH_2 failed to afford the desired hydrazone that would yield our target molecule, **10**.

An alternative approach was the formation of the dithiane **9** from ketone **8**, which would be subsequently reduced with Ni-Raney. However, again, reaction of **8** with bistrimethylsilylethanedithiol did not lead to the requested intermediate.

Those results confirm the difficulty to access to the carbonyl group in **8**.

Finally, the Barton/McCombie[13] radical deoxygenation was the chosen procedure. Consequently, alcohol **7** was first converted into the xanthate **11**. Treatment of **11** with tri-*n*-butyl tin hydride in refluxing toluene yielded compound **10**.

Selective deprotection of **10** with *p*-TsOH/MeOH and subsequent oxidation of the resulting benzylic alcohol with PDC/DMF led to aldehyde **13**. Further oxidation of **13** with sodium chlorite and removal of the remaining protecting group afforded compound **3** (Scheme 5).

The spectroscopic data of **3**, as well as its optical rotation $[\alpha]_D^{22}$ +8.5 (*c* 0.20, MeOH) are identical to those described for the natural product (+)-makassaric acid,[5] $[\alpha]_D^{22}$ +7.3 (*c* 0.54, MeOH).

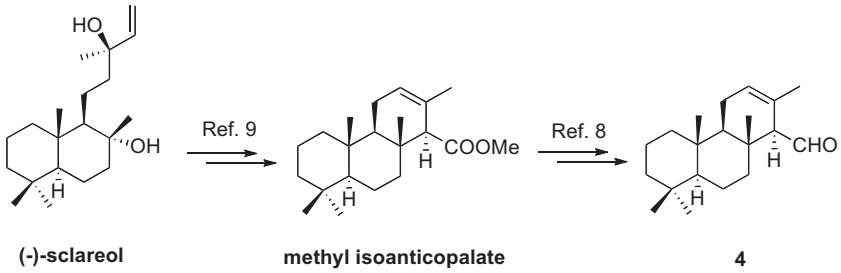
3. Conclusions

It can be concluded that this is the first, short and efficient synthesis of (+)-makassaric acid, a highly promising protein kinase MK2 inhibitor. The synthesis is very versatile and can lead to the synthesis of many analogues of (+)-makassaric acid to carry out SAR studies, aimed to improve their activity.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FTIR or an AVATAR 370 FTIR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (*J*) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast

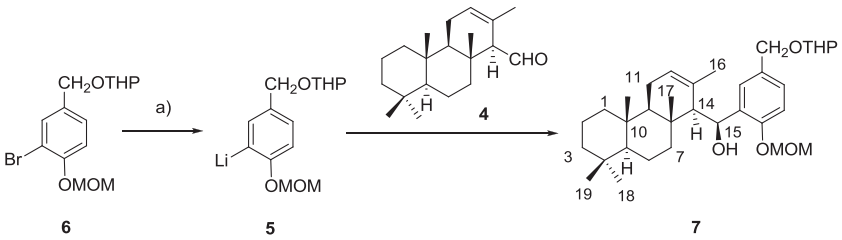


Scheme 2. Synthesis of the diterpenic moiety.

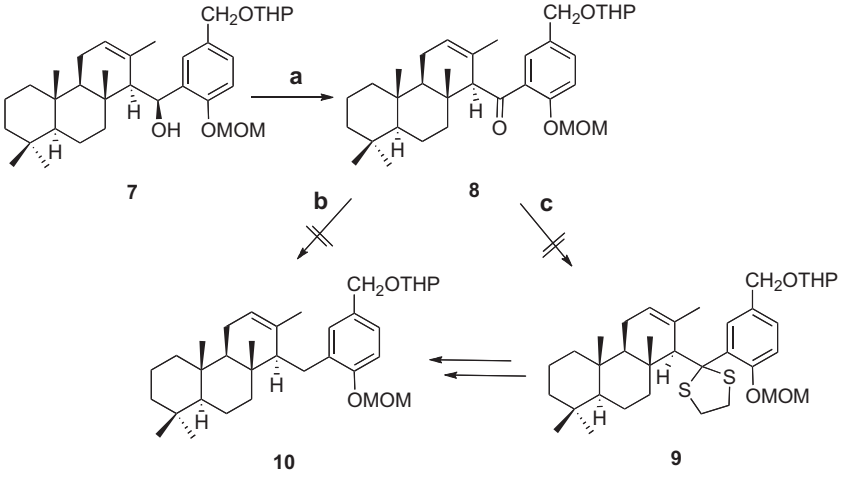
Compound **5** can be obtained by lithiation of the bromoderivative **6**, as previously mentioned (Scheme 1). This compound had already been used by us in the synthesis of (+)-subersic acid.[4]

The coupling of **4** and the lithium derivative **5** was accomplished through a nucleophilic addition. Treatment of **6** with *t*-BuLi led to the lithiated arene unit, which was added 'in situ' to the aldehyde **4** (Scheme 3).

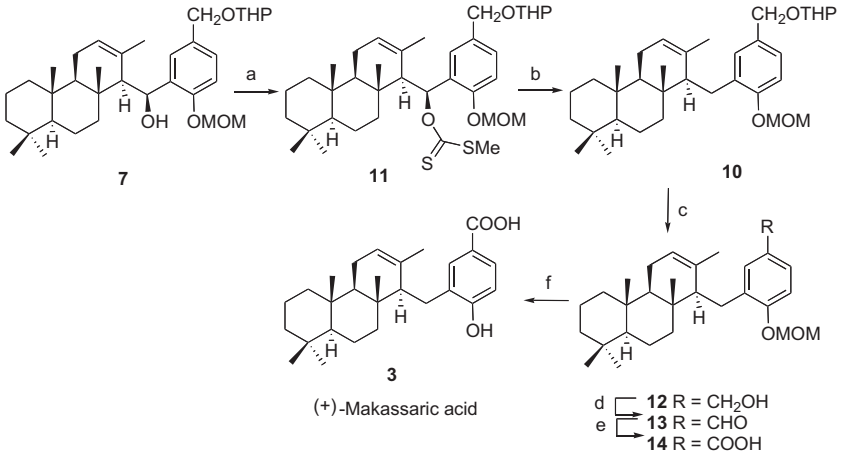
In these conditions alcohol **7** was obtained in quantitative yield. The reaction took place with total diastereofacial selection, leading only to the expected Felkin-Anh diastereoisomer.



Scheme 3. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, 3 h, 100%.



Scheme 4. Reagents and conditions: (a) TPAP, NMO, DCM, molecular sieves 4 Å, 1.5 h, 100%; (b) KOH/H_2NNH_2, ethylene glycol, 175 °C, 20 h, 230 °C, 3 h; (c) ZnI_2, 1,2-bis-trimethylsylilethanedithiol, Et_2O, −20 °C to rt.



Scheme 5. Reagents and conditions: (a) NaHMDS, CS_2, MeI, THF, −78 °C, (100%); (b) AIBN, *n*-Bu_3SnH, 120 °C, 1.5 h, (67%); (c) *p*-TsOH, MeOH, 2.5 h, rt, (85%); (d) PDC, DMF, 14 h, rt, (100%); (e) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4, 2 h, rt, (86%); (f) HCl 6 M, THF, 4 h, 50 °C, (65%).

Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin/Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Coupling reaction of 4 and 6 to yield 7

To a solution of **6** (730 mg, 2.2 mmol) in THF (7 mL), a solution of *t*-BuLi in pentane (1.7 M mg, 1.94 mL, 3.1 mmol) was added, under argon atmosphere and at −78 °C. After 15 min, a solution of **4** (133 mg, 0.46 mmol) in THF (4.1 mL) was added via cannula. After stirring for 3 h, saturated NH_4Cl was added, and the reaction mixture was extracted with EtOAc. The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude was a yellowish oil that was purified by chromatography on silica gel, affording **7** (144 mg, 100%).

4.2.1. Compound **7**. IR (film): 3473, 2940, 1727, 1612, 1587, 1511, 1464, 1386, 923, 816 cm^{-1}; ^1H NMR (400 MHz) δ: 7.65 (1H, d, J=1.6 Hz), 7.18 (1H, dd, J=8.0, 1.6 Hz), 7.03 (1H, d, J=8.0 Hz), 5.55 (1H, s), 5.30 (1H, s), 5.20 (2H, s), 4.72 (1H, d, J=11.7 Hz), 4.65 (1H, m), 4.46 (1H, d, J=11.7 Hz), 3.92 (1H, m), 3.53 (1H, m), 3.47 (3H, s), 2.65 (1H, s), 2.30–2.15 (2H, m), 1.95–0.98 (18H, m), 1.55 (3H, s), 1.13 (3H, s), 0.94 (3H, s), 0.88 (3H, s), 0.84 (3H, s), OH not observed; ^{13}C NMR

(100 MHz) δ: 153.0, 134.2, 132.8, 130.5, 128.1, 127.3, 126.6, 113.0, 97.1, 93.7, 68.5, 67.3, 62.1, 59.0, 56.7, 56.2, 55.3, 41.9, 41.7, 40.1, 38.0, 37.3, 33.4, 33.1, 30.5, 25.5, 24.6, 22.3, 21.7, 19.4, 19.0, 18.5, 16.3, 16.2; EIHRMS: calcd for $C_{34}H_{52}O_5Na$ (M+Na): 563.3707, found 563.3714.

4.3. Oxidation of 7 with TPAP to yield 8

To a solution of **7** (36 mg, 6.58 mmol) in DCM (1.42 mL), 4 Å molecular sieves (61 mg, 500 mg/mmol), NMO (30 mg, 0.22 mmol) and TPAP (4 mg, 6.4 mmol) were added. The reaction mixture was stirred at room temperature. After 1.5 h the reaction had finished according to TLC. Then, it was diluted with DCM and filtered over silica gel and Celite™. The solvent was removed under pressure to yield **8** (51 mg, 100%).

*4.3.1. Compound **8**.* IR (film): 2937, 2848, 1679 cm^{-1}; ^1H NMR (400 MHz) δ: 7.40 (1H, dd, *J*=9.2, 2.0 Hz), 7.39 (1H, d, *J*=2.0 Hz), 7.13 (1H, d, *J*=9.2 Hz), 5.56 (1H, s), 5.28 (1H, d, *J*=6.8 Hz), 5.20 (1H, d, *J*=6.8 Hz), 4.72 (1H, d, *J*=12.0 Hz), 4.65 (1H, m), 4.47 (1H, d, *J*=12.0 Hz), 4.22 (1H, s), 3.89 (1H, m), 3.50 (1H, m), 3.48 (3H, s), 1.95–0.90 (20H, m) 1.64 (3H, s), 0.91 (3H, s), 0.88 (3H, s), 0.78 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz) δ: 205.7, 154.1, 133.9, 131.8, 131.7, 131.3, 129.1, 124.2, 114.8, 97.6, 94.3, 67.9, 67.1, 62.3, 56.4, 56.3, 54.8, 42.8, 41.8, 39.7, 38.5, 37.6, 33.4, 33.2, 30.5, 25.4, 22.6, 21.9, 21.6, 19.4, 18.5, 18.4, 15.8, 15.6; EIHRMS: calcd for $C_{34}H_{50}O_5Na$ (M+Na): 561.3550, found 561.3552.

4.4. Reaction of 7 with CS_2 to yield 11

To a solution of **7** (11 mg, 0.02 mmol) in THF (0.45 mL), cooled to −78 °C, sodium hexamethyldisylazide (1.0 M in THF, 0.68 mL, 0.68 mmol) was added under argon atmosphere. The reaction mixture was stirred for 30 min at 0 °C and then CS_2 (0.1 ml, 1.71 mmol) was added. The reaction mixture is stirred for 2.5 h longer and after this time MeI (0.1 ml, 1.18 mmol) was added. It was allowed to stir during 2 h and then it was quenched with ice and extracted with EtOAc. The organics were washed with HCl 0.5 M and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel affording the desired compound **11** as an oil (16 mg, 100% yield).

*4.4.1. Compound **11**.* IR (film): 2924, 1496, 1441, 1198, 1059, 812, 668, 655 cm^{-1}; ^1H NMR (400 MHz) δ: 7.65 (1H, d, *J*=8.8 Hz), 7.15 (1H, dd, *J*=8.8, 2.2 Hz), 7.05 (1H, d, *J*=8.8 Hz), 5.57 (1H, s), 5.25 (1H, s), 5.23 (1H, s), 4.68 (1H, d, *J*=11.8 Hz), 4.64 (1H, m), 4.44 (1H, d, *J*=11.8 Hz), 3.90 (1H, m), 3.56 (1H, m) 3.50 (3H, s), 2.65 (1H, s), 2.40 (1H, m), 2.36 (3H, s), 1.85–0.85 (19H, m), 1.64 (3H, s), 1.35 (1H, m) 1.04 (3H, s), 0.91 (3H, s), 0.87 (3H, s), 0.83 (3H, s); ^{13}C NMR (100 MHz) δ: 189.2, 153.6, 132.5, 132.0, 130.7, 130.4, 127.8, 126.6, 113.2, 96.9, 93.8, 68.3, 62.1, 59.1, 56.6, 56.2, 55.9, 42.5, 41.8, 41.6, 40.1, 38.9, 37.4, 33.4, 33.1, 30.6, 25.5, 24.9, 22.6, 21.6, 19.4, 19.0, 18.5, 16.2, 15.9, 13.0; EIHRMS: calcd for $C_{36}H_{54}O_5S_2Na$ (M+Na): 653.3305, found 653.3327.

4.5. Reaction of 11 with *n*-Bu_3SnH to yield 10

To a solution of **11** (18 mg, 0.03 mmol) in toluene (0.44 mL), AIBN (1 mg, 0.027 mmol) and *n*-Bu_3SnH (0.1 ml, 0.37 mmol) were added. The reaction mixture was stirred under argon atmosphere and at 120 °C for 1.5 h. Then it was cooled down and directly subjected to chromatography on silica gel to obtain **10** (10 mg, 67%) as a colourless oil.

*4.5.1. Compound **10**.* ^1H NMR (200 MHz) δ: 7.10 (1H, d, *J*=1.8 Hz), 7.10 (1H, dd, *J*=1.8, 8.8 Hz), 7.02 (1H, d, *J*=8.8 Hz), 5.37 (1H, s), 5.19 (2H, s), 4.70 (1H, d, *J*=11.8 Hz), 4.69 (1H, m), 4.45 (1H, d, *J*=11.8 Hz), 3.90 (1H, m), 3.57 (1H, m) 3.48 (3H, s), 2.77 (1H, dd, *J*=14.0, 8.0 Hz), 2.60 (1H, dd, *J*=14.0, 2.0 Hz), 2.41 (1H, dd, *J*=8.0, 2.0 Hz), 1.98–0.85 (20H, m), 1.55 (3H, s), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s), 0.83 (3H, s).

4.6. Reaction of 10 with *p*-TsOH to yield 12

A solution of **10** (62 mg, 0.12 mmol) in *p*-TsOH/MeOH (25%, 15 mL) was stirred at room temperature during 2.5 h. The reaction was monitored by TLC and when it finished, water was added and it was extracted with EtOAc. The organic phase was washed with $NaHCO_3$ 6% and brine. It was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The desired compound **12** (44 mg, 85% yield) was obtained as a colourless oil.

*4.6.1. Compound **12**.* IR (film): 3373, 2929, 2847, 1740, 1609, 1499, 1448, 1384, 1244, 1151, 1009, 922, 821 cm^{-1}; ^1H NMR (400 MHz) δ: 7.28 (1H, d, *J*=1.7 Hz), 7.12 (1H, dd, *J*=8.4, 1.7 Hz), 7.03 (1H, d, *J*=8.4), 5.35 (1H, s), 5.19 (2H, s), 4.60 (2H, d, *J*=6 Hz), 3.49 (3H, s), 2.79 (1H, dd, *J*=15.2, 9.6 Hz), 2.59 (1H, dd, *J*=15.2, 1.6 Hz), 2.41 (1H, dd, *J*=9.6, 1.6 Hz), 2.0 (1H, m), 1.90 (2H, m), 1.70–0.85 (10H, m), 1.42 (3H, s), 1.25 (1H, m), 0.91 (3H, s), 0.89 (3H, s), 0.88 (3H, s), 0.83 (3H, s), OH not observable; ^{13}C NMR (100 MHz) δ: 154.5, 135.4, 133.8, 133.1, 128.5, 125.3, 122.0, 114.0, 94.6, 65.3, 56.2, 56.1, 55.2, 54.8, 42.0, 41.1, 39.9, 37.3, 37.0, 33.4, 33.1, 25.7, 22.7, 22.1, 21.7, 18.9, 18.5, 15.6, 14.7; EIHRMS: calcd for $C_{29}H_{44}O_3Na$ (M+Na): 463.3183, found 463.3173.

4.7. Oxidation of 12 with PDC to yield 13

To a solution of **12** (17 mg, 0.04 mmol) in DMF (1 mL), PDC (105 mg, 0.28 mmol) was added, and it was stirred under argon atmosphere for 14 h at room temperature. Then it was cooled with ice and water was added. After extraction with EtOAc, the organic phase was dried over Na_2SO_4 and the solvent was evaporated, yielding **13** (23 mg, 100% yield).

*4.7.1. Compound **13**.* ^1H NMR (200 MHz) δ: 9.9 (1H, s), 7.82 (1H, d, *J*=2.0 Hz), 7.65 (1H, dd, *J*=8.0, 2.0 Hz), 7.18 (1H, d, *J*=8.0 Hz), 5.35 (1H, s), 5.29 (2H, s), 3.50 (3H, s), 2.70 (1H, dd, *J*=15.2, 9.6 Hz), 2.59 (1H, dd, *J*=15.2, 1.6 Hz), 2.47 (1H, dd, *J*=9.6, 1.6 Hz), 2.01–0.85 (14H, m), 1.39 (3H, s), 0.91 (3H, s), 0.89 (3H, s), 0.88 (3H, s), 0.83 (3H, s).

4.8. Oxidation of 13 with $NaClO_2$ to yield 14

To a solution of **13** (22 mg, 0.05 mmol) in *t*-BuOH (0.65 mL) and 2-metyl-2-butene (0.13 mL), 0.18 mL of a solution of NaH_2PO_4 (6 g in 44 mL H_20) and $NaClO_2$ 5% (0.12 mL, mmol) were added. The solution was stirred for 2 h at room temperature. After this time it was acidulated with HCl 2 N and extracted with Et_2O. The organics were washed with water and dried over Na_2SO_4. After removal of the solvent, compound **14** (19 mg, 86% yield) was obtained as a colourless oil.

*4.8.1. Compound **14**.* IR (film): 2928, 2852, 1686, 1604,1499,1265, 1080, 923, 735 cm^{-1}; ^1H NMR (400 MHz) δ: 8.03 (1H, d, *J*=1.9 Hz), 7.09 (1H, dd, *J*=8.6, 1.9 Hz), 7.10 (1H, d, *J*=8.6 Hz), 5.35 (1H, s), 5.27 (2H, s), 3.51 (3H, s), 2.79 (1H, dd, *J*=15.5, 9.6 Hz), 2.62 (1H, dd, *J*=15.5, 1.6 Hz), 2.45 (1H, dd, *J*=9.6, 1.6 Hz), 2.05–0.85 (14H, m), 1.40 (3H, s), 0.91 (3H, s), 0.89 (3H, s), 0.89 (3H, s), 0.82 (3H, s), COOH not observable; ^{13}C NMR (100 MHz) δ: 171.7, 159.3, 135.0, 133.0, 131.6, 129.3, 122.3, 122.1, 113.0, 94.2, 56.4, 56.0, 55.1, 54.5, 41.1, 41.9, 39.9, 37.3, 37.0, 33.4, 33.1, 25.7, 22.7, 22.2, 21.7, 18.9, 18.6, 15.6, 14.7; EIHRMS: calcd for $C_{29}H_{42}O_4Na$ (M+Na): 477.2975, found 477.2958.

4.9. Reaction of 14 with HCl 6 M to yield makassaric acid

To a solution of **14** (20 mg, 0.04 mmol) in THF (0.5 mL), 0.5 mL of HCl 6 M were added and the reaction mixture was stirred for

4 h at 50 °C. When the reaction finished it was allowed to reach room temperature and then poured over a saturated solution of NaCl. The mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The crude was purified by chromatography on silica gel to afford **3** (12 mg, 65% yield). The data were coincident with the ones of (+)-makassaric acid.

*4.9.1. Makassaric acid (**3**).* $[\alpha]_D^{20}$ +6.5 (*c* 0.2, $CHCl_3$); $[\alpha]_D^{20}$ +8.5 (*c* 0.2, MeOH); IR (film): 3368, 2927, 2850, 1683, 1603, 1442, 1385, 1276 cm^{-1}; ^1H NMR (400 MHz) δ: 8.02 (1H, d, *J*=1.8 Hz), 7.82 (1H, dd, *J*=8.3, 1.8 Hz), 6.78 (1H, d, *J*=8.3 Hz), 5.36 (1H, s), 2.67 (1H, dd, *J*=15.0, 9.5 Hz), 2.64 (1H, d, *J*=15.0 Hz), 2.47 (1H, s), 2.05–0.85 (14H, m), 1.41 (3H, s), 0.92 (3H, s), 0.89 (3H, s), 0.89 (3H, s), 0.82 (3H, s), signals for COO*H* and O*H* are not visible; ^{13}C NMR (100 MHz) δ: 171.3, 158.2, 134.7, 132.3, 130.1, 129.3, 122.5, 121.5, 115.1, 56.0, 55.0, 54.1, 41.9, 41.1, 39.8, 37.2, 37.0, 33.4, 33.1, 25.7, 22.7, 22.3, 21.7, 18.9, 18.5, 15.6, 14.7; EIHRMS: calcd for $C_{27}H_{38}O_3$ (M^+): 410.2743, found 410.2748.

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