



Guanacastepene-A total synthesis: construction of the tricyclic *iso*-guanacastepane, *epi*-guanacastepane and guanacastepane frameworks

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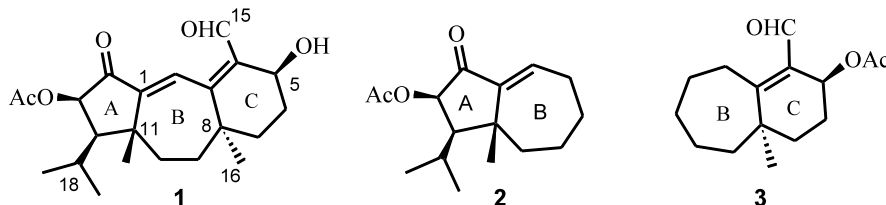
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Abstract—Studies aimed towards the total synthesis of the diterpene antibiotic, guanacastepene A, of current interest and displaying promising biological activity against drug resistant pathogens has led to the generation of some novel tricyclic skeletal replete with extensive functionalization and representing interesting variations of the guanacastepane framework. © 2003 Elsevier Science Ltd. All rights reserved.

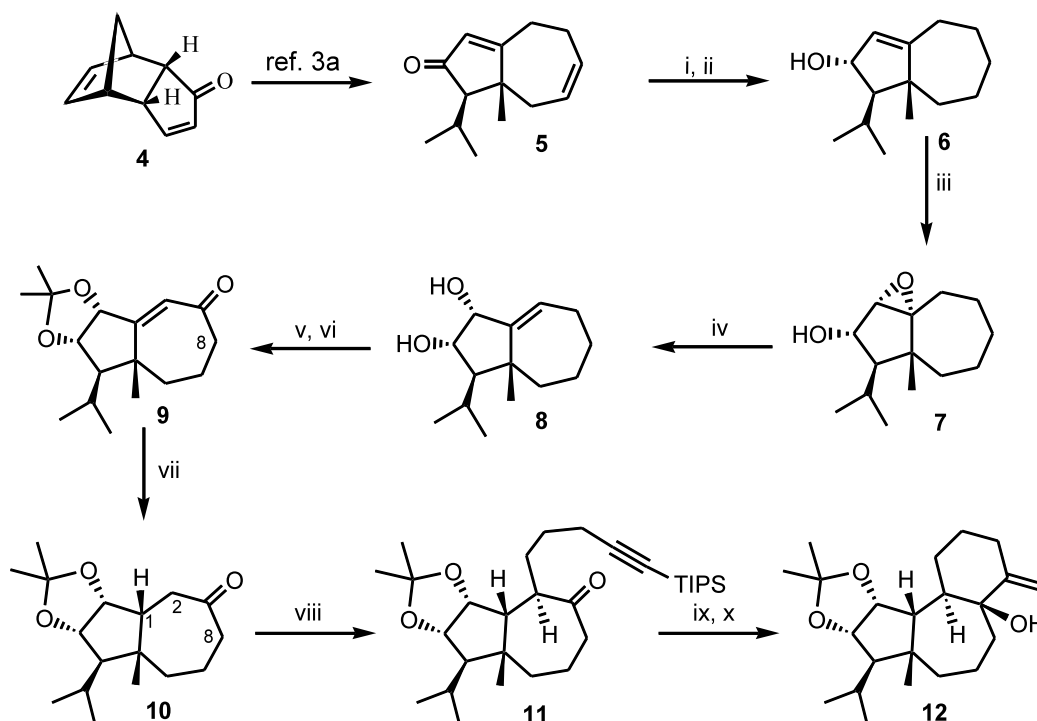
Guanacastepene A **1**, a diterpene with a novel carbon skeleton (guanacastepane), was isolated from an unidentified endophytic fungus growing on the tree *Daphnopsis americana* by Clardy et al.^{1a} in 2000 and its structure was determined by X-ray crystallography. More recently, several additional guanacastepenes B–O have been isolated from the same fungus and structurally characterized.^{1b} Guanacastepene A **1** has been shown to exhibit impressive activity against methicillin-resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus faecium*. Additional, biological studies on **1** have unravelled moderate activity against Gram-positive bacteria, poor activity against Gram-negative bacteria and haemolytic activity against human RBC.^{1c} While these latter attributes undermine the therapeutic potential of **1**, its promising profile against MRSA and VREF has stimulated an intensive world-wide search for synthetic and naturally occurring analogues.

The 5,7,6-ring fused tricyclic framework of **1**, with attendant network of functionalities and stereochemical subtleties, makes it a formidable synthetic

target. Thus, on account of its biological potential and synthetic challenge, nearly a dozen research groups have been enticed into the fray^{2–4} in the quest for guanacastepene A **1**. While Danishefsky et al.⁴ have been the first to reach the milestone and achieved a total synthesis of **1** in 2002, others have unfolded strategies leading to the acquisition of bicyclic and tricyclic core structures of **1**.^{2–4} We too have entered this arena and reported model studies^{3a} leading to the bicyclic hydroazulenic core of guanacastepene A and further extended^{3b} these studies to acquire its fully functionalized and stereochemically secured AB and BC ring segments, **2** and **3**, respectively. Our synthetic approach towards **1**, from the beginning, was aimed at imparting substantial structural, functional and stereochemical latitude to enable access to diverse analogues of the natural product in view of its biological potential. Herein, we report our further synthetic explorations in the area that have resulted in the acquisition of tricyclic *iso*-guanacastepane, *epi*-guanacastepane and guanacastepane derivatives, representing novel skeletal and functional group analogues and variants of **1**.



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Scheme 1. Reagents and conditions: (i) 10% Pd/C, H₂, EtOAc, 98%; (ii) DIBAL-H, DCM, 98%; (iii) MCPBA, DCM, 92%; (iv) pyridine, TMSOTf, DMAP, 75–80%; (v) DMP, acetone, PPTS, 95%; (vi) 3,5-dimethylpyrazole, CrO₃, DCM, 50%; (vii) 10% Pd/C, H₂, EtOAc, 80%; (viii) LDA, THF, HMPA, I(CH₂)₃CCTIPS, –78°C–rt, 12 h, 30%; (ix) TBAF, moist THF, rt, 95%; (x) Na-naphthalenide, THF, 90%.

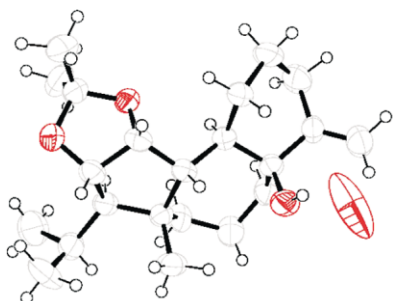


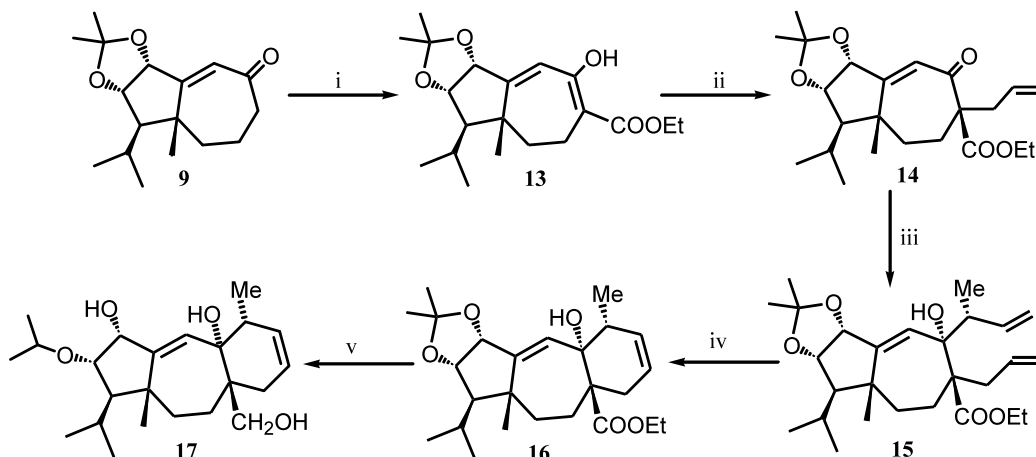
Figure 1.

Our first foray was targeted towards the construction of the tricyclic guanacastepane skeleton by annulation of a six-membered ring onto a hydroazulenenic precursor following the earlier^{3b} model study that led to the realization of 3. However, the implementation of the projected reaction sequence resulted in a regiochemical deviation and led to the novel isoguanacastepane skeleton. Hydroazulenenic enone 5, readily available through a short sequence^{3a} from tricyclic enone 4 was elaborated to 6 through selective catalytic hydrogenation of the isolated double bond and stereoselective enone reduction (Scheme 1). This stereoselective reduction is somewhat anomalous with hydride addition exclusively from the same face as the β -isopropyl and β -methyl groups and is in accordance with earlier observations in similar systems.^{3a,4} Stereoselective epoxidation of 6 led to 7 and TMSOTf mediated epoxide opening furnished the *cis*-enediol 8 (Scheme 1).⁵ Acetonide protection of the

cis-diol in 8 and allylic oxidation⁶ furnished 9⁵ in which we had a versatile precursor that had in place the key oxy-functionalization in the A-ring and the olefinic bond in the B-ring as required in the natural product 1. Therefore the main task ahead was the annulation of the six-membered C-ring and for this purpose several strategies (vide infra) were explored.

Repeated efforts to alkylate 9 at the desired C-8 position with *tris*-isopropylsilyl protected 5-iodo-1-pentyne or other alkylating agents to set-up the planned six-ring annulation^{3b} proved abortive. While this effort was in progress others also reported similar observations.^{2,4} Recourse was then taken to the reduced product 10 of 9, which could be alkylated regioselectively with *tris*-isopropylsilyl protected 5-iodo-1-pentyne to furnish 11⁵ via C-2 alkylation rather than at the required C-8 position (Scheme 1). Silyl deprotection of 11 and sodium naphthalenide mediated intramolecular alkyne-ketone cyclization^{3b} proceeded with excellent stereoselectivity and in high yield to furnish 12 (Scheme 1). A single crystal X-ray structure determination⁷ of 12 confirmed the site of alkylation in 10 and consequent acquisition of the new 5,7,6-fused tricyclic (*iso*-guanacastepane) skeleton (Fig. 1).

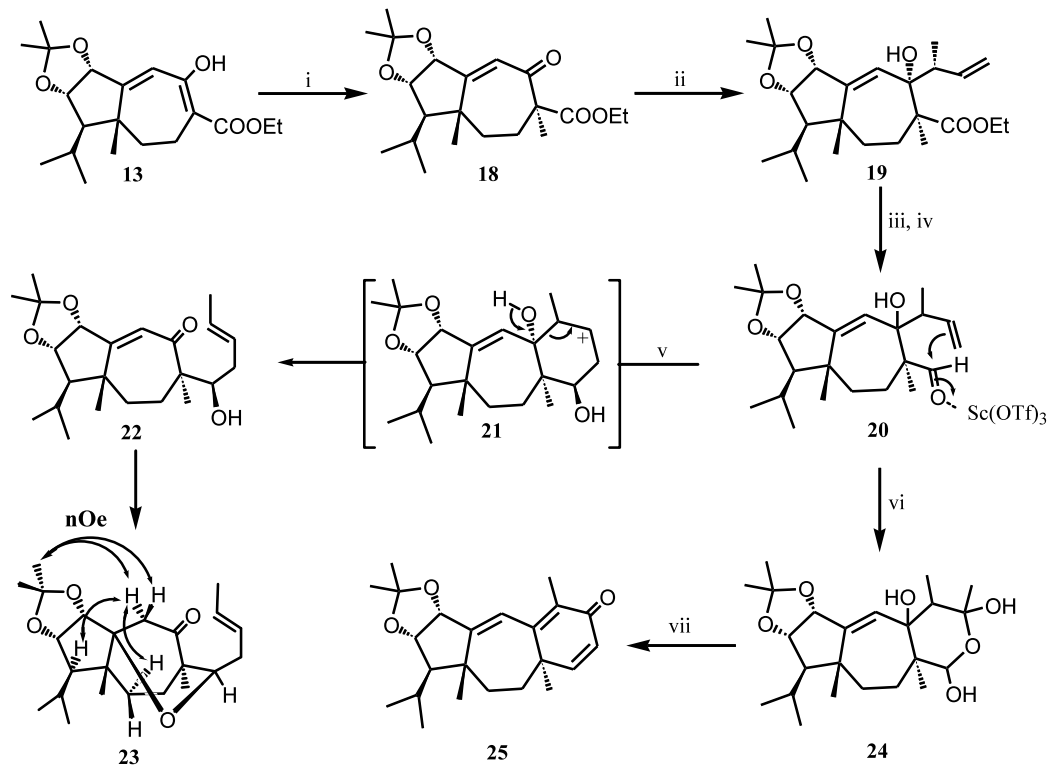
Attention was now turned to address the crucial issue of alkylation of the enone 9 at the C-8 position. It was observed that 9 could be α -carboethoxylated at the C-8 position employing Mander's reagent⁸ to yield 13, which could be further allylated stereoselectively (vide infra) and in good yield to 14 (Scheme 2). Addition of



Scheme 2. Reagents and conditions: (i) LDA, THF-HMPA, CNCOOEt, -78°C, 75%; (ii) NaH, THF, allyl bromide, rt, 95%; (iii) Mg, 3-chloro-1-butene, CeCl₃, THF, 60%; (iv) Grubbs' catalyst (10 mol%), benzene, Δ, 96%; (v) DIBAL-H, DCM, 65%.

the Grignard reagent prepared from 3-chloro-1-butene to **14** in the presence of cerium(III) chloride⁹ proceeded stereoselectively to furnish **15**⁵ and set the stage for the contemplated RCM protocol for the construction of the six-membered C-ring of guanacastepene (Scheme 2). Indeed, exposure of **15** to Grubbs' catalyst resulted in smooth conversion to the tricyclic compound **16** in high yield (Scheme 2).⁵ Reduction of **16** with DIBAL-H resulted not only in the reduction of the ester functionality to a primary alcohol but quite unexpectedly also

reductively cleaved the acetonide moiety to yield **17** (Scheme 2). An X-ray crystal structure determination⁷ of **17** firmly established its stereochemistry and indicated that it was epimeric at C-8 with respect to the natural guanacastepenes and that the allylation of **13** had preferentially occurred from the less hindered α-face. However, in a short sequence it was possible to transform the bicyclic ketone **9** into the C₂₀-skeleton corresponding to *epi*-guanacastepene with a rich complement of functionalities in all the three rings (Fig. 2).



Scheme 3. Reagents and conditions: (i) NaH, THF, MeI, 85–90%; (ii) Mg, 3-chloro-1-butene, CeCl₃, THF, 70%; (iii) LAH, THF, rt, 75%; (iv) TPAP, NMMO, 4 Å MS, 70%; (v) Sc(OTf)₃ (catalytic), DCM, 60–70%; (vi) PdCl₂, CuCl, O₂, DMF-H₂O, 85%; (vii) NaOEt, EtOH, rt, 40–50%.

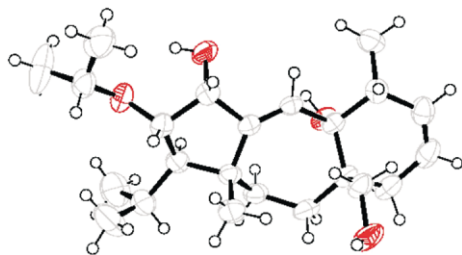


Figure 2.

The epimeric nature of **17** at C-8 indicated that the way to generate the correct stereochemistry present in the natural guanacastepenes was to harness the carboethoxy group in **13** in the C-ring forming protocols. Towards this end **13** was methylated to furnish **18** and correctly install the C-8 quaternary centre with the methyl group in the α -orientation and *trans* with respect to the pre-existing C-11 angular methyl group (Scheme 3). Addition of the Grignard reagent derived from 3-chloro-1-butene to **18** in the presence of cerium(III) chloride was chemoselective and furnished **19**.⁵ The ester group in **19** was now elaborated via LAH reduction and *n*-tetrapropylammonium per-ruthenate (TPAP) oxidation to aldehyde **20**,⁵ in preparation for its integration into the proposed six-membered ring. For this purpose, an intramolecular Prins-type cyclization in **20** with several Lewis acids was explored but without much success. We therefore turned to a recent report where $\text{Sc}(\text{OTf})_3$ had been found to be effective in inducing aldehyde-ene cyclization.¹⁰ Consequently, **20** was exposed to $\text{Sc}(\text{OTf})_3$ and the reaction took an interesting course. We found that **22**, a *seco*-guanacastepene derivative, was formed first via the fragmentation of the initially generated aldehyde-ene cyclization intermediate **21**. Continued exposure of **22** to the reaction milieu resulted in further intramolecular cyclization to the interesting bridged ether **23**,⁵ whose stereostructure was secured through detailed 2D NMR (COSY, NOE) studies (Scheme 3). As a consequence of this unanticipated albeit interesting deviation, we had to alter our strategy. Wacker oxidation of the terminal olefinic bond in **20** led to the hydrate **24**, an appropriate candidate for effecting aldol cyclization to generate the C-ring of guanacastepenes. In the event, stirring **24** with sodium ethoxide in ethanol led to the desired cyclization and concomitant dehydration to yield an extremely interesting cross conjugated trienone **25**⁵ with the complete guanacastepene framework and a high level of functionalization (Scheme 3). It is to be noted that the cross-conjugated trienone functionality present in **25** is quite unique and may impart some useful biological attributes to this molecule.

In summary, we have achieved a synthesis of the 5,7,6-fused tricyclic framework of guanacastepene diterpenes, replete with requisite stereochemical features and extensive functionalization, from a hydroazulenenic precursor with the focus on the exploration of different six-ring annulation strategies. Our efforts have also provided

access to new tricyclic structural variants (*iso*-guanacastepene and *epi*-guanacastepene) of the biologically promising guanacastepene **A 1**.

Acknowledgements

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References

- (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116; (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900; (c) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256.
- (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569; (b) Dudley, G. B.; Danishefsky, S. *Org. Lett.* **2001**, *3*, 2399; (c) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789; (d) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947; (e) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123; (f) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063; (g) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033; (h) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469; (i) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363; (j) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959; (k) Magnus, P.; Ollivier, C. *Tetrahedron Lett.* **2002**, *43*, 9605.
- (a) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063; (b) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975.
- (a) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185; (b) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188.
- All new compounds reported here are racemic and were duly characterized on the basis of spectral (IR, ¹H and ¹³C NMR) and analytical data. Selected spectral data: **Compound 12**: IR (cm⁻¹): 3449, 1645; ¹H NMR (300 MHz, CDCl₃): δ 4.99 (s, 1H), 4.77 (s, 1H), 4.42–4.31 (m, 2H), 2.24–2.07 (m, 4H), 1.90–1.84 (m, 2H), 1.72–1.50 (series of m, 8H), 1.49 (s, 3H), 1.27 (s, 3H), 1.27–1.25 (m, 1H), 1.16–1.08 (m, 1H), 1.02–1.00 (brs, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 158.6, 109.5, 107.0, 82.2, 82.1, 60.7, 51.8, 46.7, 43.4, 42.9, 39.3, 29.5, 28.8, 26.4, 26.2, 26.0, 25.4, 24.3, 23.5, 21.2, 19.2. **Compound 16**: IR (cm⁻¹): 3519, 1730; ¹H NMR (300 MHz, CDCl₃): δ 5.84 (d, *J*=1.5 Hz, 1H), 5.63–5.58 (m, 1H), 5.35 (brd, *J*=10.2 Hz, 1H), 4.87 (d, *J*=7.2 Hz, 1H), 4.37 (dd as t, *J*=7.2 Hz, 1H), 4.05 (q, *J*=7.5 Hz, 2H), 2.84–2.82 (m, 1H), 2.51–2.41 (m, 2H), 2.34 (dd, *J*=18.6, 3.0 Hz, 1H), 2.67–2.20 (m, 1H), 1.85–1.82 (m, 1H), 1.78 (brs, 1H), 1.74–1.66 (m, 1H), 1.48 (s, 3H), 1.43–1.36 (m, 1H), 1.36 (s, 3H), 1.20 (t, *J*=7.5 Hz, 3H), 1.12 (d, *J*=7.2 Hz, 3H), 1.04 (d,

$J=6.6$ Hz, 3H), 0.98 (d, $J=6.6$ Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 175.8, 150.6, 131.6, 125.5, 123.6, 112.4, 82.8, 80.2, 72.6, 61.6, 60.2, 54.1, 49.5, 40.2, 37.0, 36.7, 33.8, 28.1, 27.9, 26.2, 23.6, 22.4, 18.8, 14.0, 13.9; HRMS calcd for: $\text{C}_{25}\text{H}_{38}\text{O}_5\text{Na}$ (MNa^+): 441.2671. Found: 441.2629. **Compound 20**: IR (cm^{-1}): 3494, 1713; ^1H NMR (300 MHz, CDCl_3): δ 9.78 (s, 1H), 5.78–5.66 (m, 1H), 5.52 (s, 1H), 5.09–5.02 (m, 2H), 4.79 (d, $J=6.9$ Hz, 1H), 4.42 (dd as t, $J=7.2$ Hz, 1H), 2.89–2.79 (m, 1H), 2.53 (s, 1H), 2.04–1.99 (m, 2H), 1.90–1.85 (m, 1H), 1.80–1.68 (m, 2H), 1.64–1.59 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.08 (d, $J=6.0$ Hz, 3H), 1.07 (d, $J=6.6$ Hz, 3H), 1.04 (d, $J=6.6$ Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 207.9, 145.3, 141.1, 134.4, 117.7, 111.8, 82.0, 81.9, 81.8, 63.2, 53.3, 49.3, 47.0, 34.5, 28.3, 26.7, 26.1, 25.1, 24.6, 21.8, 20.4, 17.4, 16.6; HRMS calcd for $\text{C}_{23}\text{H}_{36}\text{O}_4\text{Na}$ (MNa^+): 399.2511. Found: 399.2500; **Compound 23**: IR (cm^{-1}): 1720, 970; ^1H NMR (400 MHz, CDCl_3): δ 5.54–5.43 (m, 2H), 4.50 (d, $J=8.0$ Hz, 1H), 4.24 (dd, $J=8.4$, 5.6 Hz, 1H), 3.76 (dd, $J=7.6$, 4.0 Hz, 1H), 2.71 (1/2ABq, $J=19.6$ Hz, 1H), 2.40 (1/2ABq, $J=19.6$ Hz, 1H), 2.22–2.15 (m, 1H), 2.00–1.88 (m, 3H), 1.72–1.67 (m, 1H), 1.65 (d, $J=4.4$ Hz, 3H), 1.62–1.58 (m, 1H), 1.47 (s, 3H), 1.37 (dt, $J=14.8$, 4.0 Hz, 1H), 1.30 (s, 3H), 1.27–1.23 (m, 1H), 1.03 (s, 6H), 0.99 (d, $J=6.4$ Hz, 3H), 0.92 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 212.1, 128.1, 127.1, 112.7, 85.3, 84.6, 82.7, 82.0, 60.3, 52.5, 51.0, 42.2, 38.7, 38.3, 34.9, 29.5, 25.9, 24.7, 22.7, 22.4, 20.4, 18.0, 16.0; HRMS calcd for: $\text{C}_{23}\text{H}_{36}\text{O}_4\text{Na}$ (MNa^+): 399.2511. Found: 399.2526. **Compound 25**: IR (cm^{-1}): 1658, 1625; ^1H NMR (400 MHz, CDCl_3): δ 6.71 (d, $J=9.6$ Hz, 1H), 6.33 (s, 1H), 6.23 (d, $J=9.6$ Hz, 1H), 4.88 (d, $J=6.4$ Hz, 1H), 4.44 (dd as t, $J=6.8$ Hz, 1H), 2.00–1.92 (m, 1H), 1.85 (s, 3H), 1.78–1.64 (m, 5H), 1.53 (s, 3H), 1.37 (s, 3H), 1.27 (s, 3H), 1.06 (d, $J=6.4$ Hz, 3H), 1.01 (d, $J=6.4$ Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 186.1, 157.2, 152.5,

132.3, 126.6 (brd), 124.4, 112.0, 82.8, 81.4 (brd), 34.5 (brd), 31.9 (brd), 29.7, 28.3, 27.4, 26.1, 24.2, 21.9, 11.5; HRMS calcd for $\text{C}_{23}\text{H}_{32}\text{O}_3\text{Na}$ (MNa^+): 379.2249. Found: 379.2268.

6. Salmond, W. G.; Barta, M. A.; Havens, H. L. *J. Org. Chem.* **1978**, 43, 2057.
7. **Crystal data for compound 12**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: monoclinic, space group: $C2/c$, cell parameters: $a=9.882$ (1), $b=21.732$ (3), $c=20.003$ (3) Å; $\beta=102.709$ (3)°; $V=4190.98$ Å³, $Z=8.0$, $F(000)=1568.0$, $\mu=0.07$ mm⁻¹, $D_{\text{calcd}}=1.13$, $\lambda=0.7107$ Å. Total number of l.s. parameters=375, $R_1=0.0874$ for 1517 $F_o>4\sigma(F_o)$ and 0.2519 for all 4213 data. GOF (S)=0.972, restrained GOF=0.972 for all data. An ORTEP diagram (with trapped water molecule) with 50% ellipsoidal probability of compound **12** is shown in Figure 1, CCDC No. 205947. **Crystal data for compound 17**: Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares using SHELXL-97. Crystal system: monoclinic, space group: $P2(1)/c$, cell parameters: $a=7.1824$ (7), $b=17.096$ (1), $c=17.994$ (1) Å; $\beta=92.759$ (2)°; $V=2207.03$ Å³, $Z=4.0$, $F(000)=832.0$, $\mu=0.08$ mm⁻¹, $D_{\text{calcd}}=1.139$, $\lambda=0.7107$ Å. Total number of l.s. parameters=396, $R_1=0.0530$ for 3070 $F_o>4\sigma(F_o)$ and 0.0664 for all 3731 data. GOF (S)=1.105, restrained GOF=1.105 for all data. An ORTEP diagram with 50% ellipsoidal probability of compound **17** is shown in Figure 2, CCDC No. 205714.
8. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, 24, 5425.
9. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392.
10. Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, C. *Tetrahedron Lett.* **1998**, 39, 1997.