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Towards the synthesis of [15]-membered stevastelins through the 2,3-epoxy analogues

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Abstract—A synthetic approach to the [15]-membered stevastelins, a novel class of immunosuppressant agents, is reported based on a macrolactamization route to the 2,3-epoxy derivative **6**. The synthesis of this compound was achieved via a stereoselective epoxidation of the allylic alcohol **13**, followed by a coupling reaction with a variety of peptide derivatives to give the epoxy peptides **7**–**10**. After an extensive study of cyclizations with these precursors, the best result was achieved with the macrolactamization of **8** in the presence of DEPC, to obtain the epoxy cyclic depsipeptide **6** in 42% yield. From this product, an epoxy analogue of stevastelin B, compound **27**, was prepared. Finally, the synthesis of the natural product was attempted through the opening of the oxirane ring contained in **6** and **26**, with a variety of methyl cuprate reagents, but without success.

The stevastelins, isolated from the culture broths of *Penicillium* sp. NK374186,[1] comprise a family of [13]- and [15]-membered cyclic depsipeptides with outstanding immunosuppressive properties (Fig. 1).[2] The particular mechanism of action exhibited by this novel class of cyclic depsipeptides, which is shared with the natural product sanglifehrin A,[3] is characterized by the inhibition of T-cell proliferation without affecting the phosphatase activity of calcineurin,[4] and is in contrast with the action displayed by the well-known immunosuppressant agents cyclosporin A[5] and FK506.[6]

Due to the biological relevance of this class of naturally occurring products, not only as potential therapeutics in transplantation surgery, but also as biochemical probes for the investigation of new signal transduction pathways,[7] the stevastelins have elicited a flurry of synthetic interest culminating with the total syntheses of stevastelin B (**2**)[8,9] and stevastelin C3 (**5**),[10] together with various synthetic approaches[11] and analogue syntheses.[3] We recently initiated a research program directed towards the syntheses of such compounds based on a macrolactonization approach which suc-

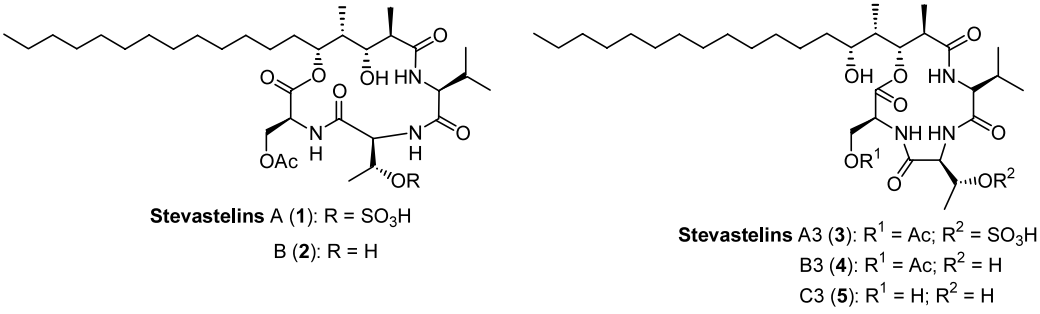

Figure 1. Structures of stevastelins A (**1**), B (**2**), A3 (**3**), B3 (**4**) and C3 (**5**).

Keywords: stevastelin; immunosuppressant; natural products; cyclic depsipeptide; stereoselective synthesis; macrolactamization.
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† With the utmost respect and sadness, we regret to inform the scientific community of Professor López Herrera's passing.

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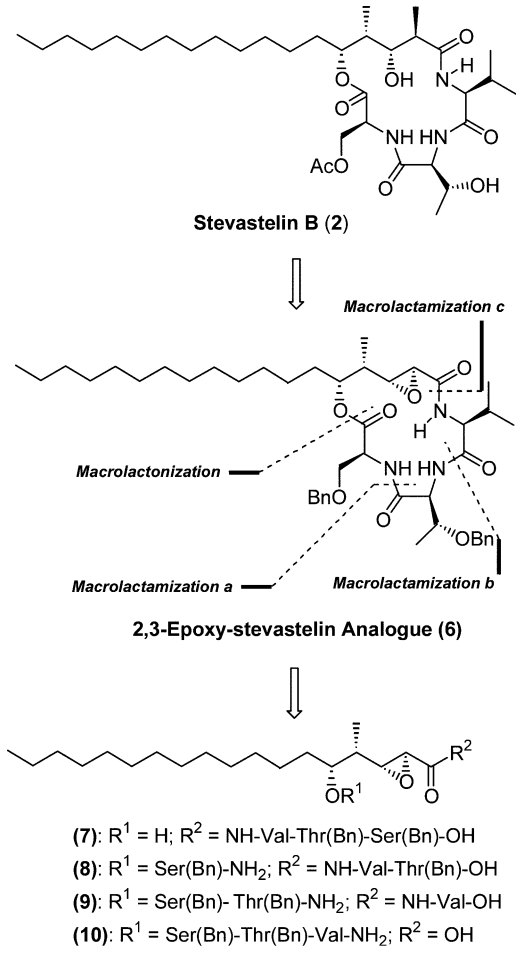
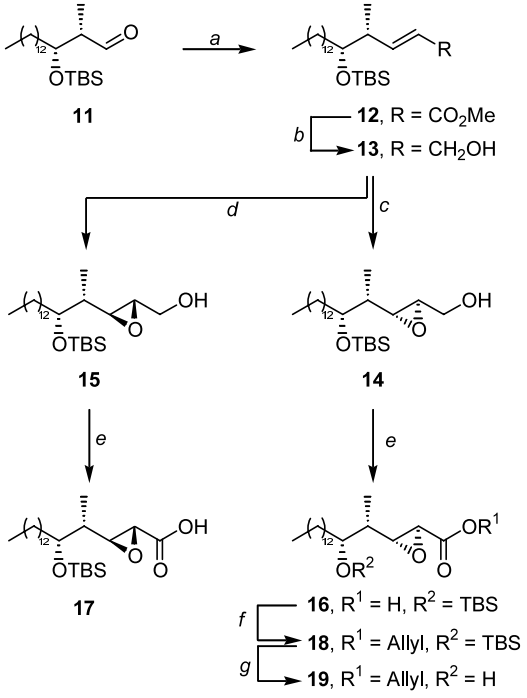
ceeded with the synthesis of the [13]-membered ring component, stevastelin C3.[10] Unfortunately, this synthetic strategy proved to be completely ineffective for the construction of the [15]-membered ring contained in stevastelin A (**1**) and B (**2**). Consequently, an alternative synthetic strategy was required for these members, that would permit: (a) an efficient and rapid construction of the [15]-membered ring, and (b) access to analogues of biological and mechanistic interest. Among a wide variety of structural and synthetic possibilities, the 2,3-epoxyamide analogue of the [15]-membered stevestalin, compound **6**, was identified as an excellent candidate that would satisfy both requisites indicated above. For the synthesis of this target compound, we decided to explore all the macrocyclization possibilities including the three possible macrolactamizations (*a*, *b* and *c*) and the macrolactonization of the corresponding epoxy-amino acids (**8**–**10**) and epoxy-hydroxy acid **7** (Scheme 1).

The synthesis commenced with the reaction of aldehyde **11**[10,12] with methyl (triphenylphosphoranylidene)acetate to give the *E* alkene **12** in a 92% yield. The DIBAL-H reduction of **12** was followed by an asymmetric Sharpless epoxidation[13] employing (−)-DET to provide epoxide alcohol **14** in very good yield (91%) but with a modest d.e. (diastereomeric excess) of 85%. This low degree of diastereoselectivity was attributed to the fact that the pairing of substrate **13** with (−)-DET constitutes a mismatched case due to the opposite stereofacial preference that both components display.[14] In fact, epoxidation of **13** with *m*-CPBA furnished epoxy alcohol **15** as the sole product in 90% yield. Both epoxy alcohols were transformed into the corresponding acids by treatment with ruthenium tetraoxide[15] to furnish the epoxy acids **16** and **17**, respectively (Scheme 2). Subsequently, the acid **16** was transformed into the allyl ester **19** in order to obtain the corresponding precursors for the macrolactamization reactions.

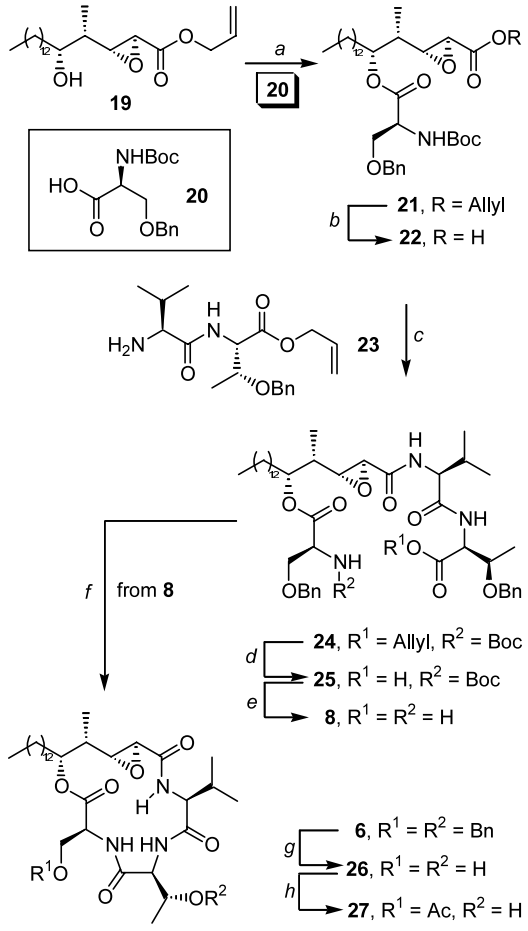
Initially, we began with the epoxy-acid with the correct configuration, **19**, which was submitted to a variety of coupling reactions with different peptide derivatives depending on the desired final macrocyclization to be executed. Scheme 3 outlines the synthesis of the key precursor **8**. Thus, the coupling of the epoxy ester **19** with the serine derivative **20** was accomplished by treatment with EDCI/DMAP to provide ester **21** in 85% yield with <2% epimerization. It is worthy to mention that other procedures such as the Yamaguchi protocol,[16] provided the desired ester **21** in 75% yield but with a 5–8% epimerization degree, most likely located at C-2 of the serine residue, whereas the Corey–Nico-



Scheme 1. Retrosynthetic analysis of stevastelin B (**2**).



Scheme 2. *Reagents and conditions*: (a) 1.5 equiv. Ph_3PCHCO_2Me, C_6H_6, 80°C, 12 h, 92%. (b) 2.2 equiv. DIBAL-H, CH_2Cl_2, −78°C, 0.5 h, 98%. (c) 1.0 equiv. D-(−)-DET, 1.0 equiv. Ti(O*i*-Pr)$_4$, 2.0 equiv. TBHP, CH_2Cl_2, −20°C, 24 h, 91% (d.e. 85%). (d) 2.0 equiv. *m*CPBA, CH_2Cl_2, 0°C, 0.5 h, 90%. (e) 4.2 equiv. $NaIO_4$, 0.05 equiv. $RuCl_3$, CCl_4, CH_3CN, H_2O, 0°C, 0.5 h, 65% for **16** and 65% for **17**. (f) 4.0 equiv. CH_2=CH-CH_2OH, 1.5 equiv. EDCI, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 2 h, 85% (d.e. 85%). (g) HF·Pyr, THF, 25°C, 12 h, 99% (d.e. 85%).



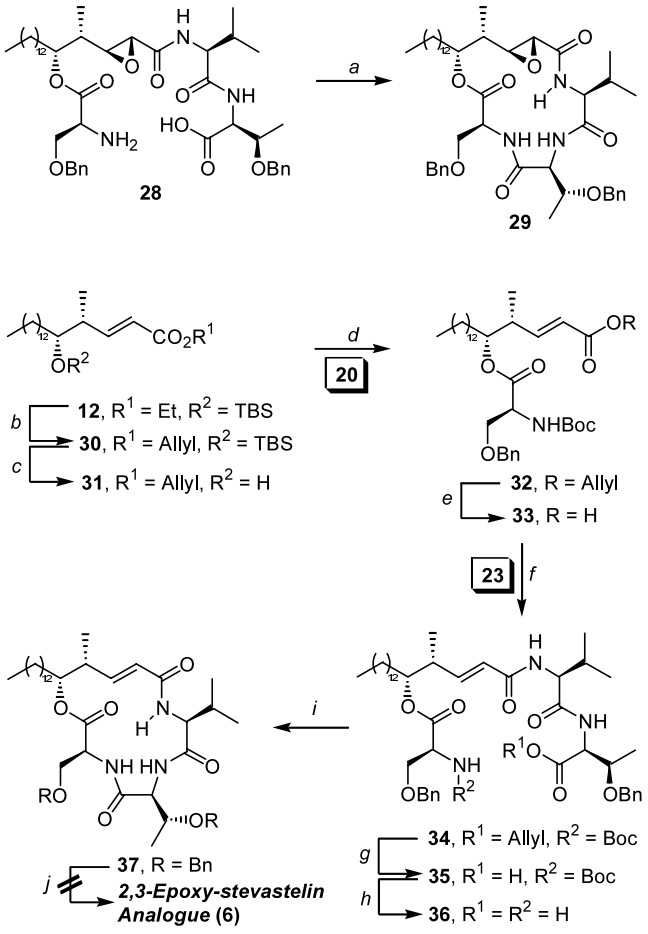
Scheme 3. *Reagents and conditions*: (a) 1.4 equiv. of **20**, 1.5 equiv. EDCI, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 2 h, 85%. (b) 0.1 equiv. $Pd(PPh_3)_4$, 5.0 equiv. morpholine, THF, 25°C, 0.5 h, 98%. (c) 1.1 equiv. of **23**, 1.5 equiv. EDCI, 1.1 equiv. HOBt, CH_2Cl_2, 25°C, 0.5 h, 89%. (d) 0.1 equiv. $Pd(PPh_3)_4$, 5.0 equiv. morpholine, THF, 25°C, 0.5 h, 97%. (e) TFA, CH_2Cl_2, 25°C, 0.5 h, 99%. (f) 2.0 equiv. DEPC, 2.0 equiv. DIPEA, DMF (2.0 mM based on **8**), 25°C, 12 h, 42%. (g) H_2, Pd–C, EtOAc/MeOH (1/1), 25°C, 2 h, 75%. (h) 6.0 equiv. Ac_2O, pyr., 0°C, 1.5 h, 60%.

laou method[17] produced a complex mixture of decomposition products. We therefore continued with compound **21**, expecting to increase the diastereomeric purity of the following compounds through successive chromatographic purifications. Compound **21** represented the common intermediate for the synthesis of the other three epoxy amino acids. Thus, conversion to the acid **22** by the action of $Pd[PPh_3]_4$ and morpholine,[18] followed by coupling with dipeptide **23** by treatment with EDCI and 1-hydroxybenzotriazole (HOBt), afforded compound **24** in 89% yield, which was transformed into the key precursor **8** by the conventional cleavage reaction. In a similar manner the other key precursors, compounds **7**, **9** and **10**, were prepared following conventional methods as described before, without significant difficulty.

With the acyclic epoxy acids **7**, **8**, **9** and **10** in hand, we proceeded with the macrocyclization studies. Due to the chemical lability of the oxirane function, we deemed it of prime importance to scan a wide array of different coupling reagents and reaction conditions to optimize the production of the targeted epoxy cyclic depsipeptide **6**. In contrast to the macrolactonization reaction of **7**, in which only the Yamaguchi protocol was investigated, for epoxy amino acids **8**, **9** and **10** a variety of reagents, solvents and conditions were surveyed for the macrolactamization reactions. From these studies, the best results were obtained when the acyclic precursor **8** was treated with pentafluorophenyl diphenylphosphinate (FDPP),[19] diphenyl phosphorazidate (DPPA)[20] or diethyl cyanophosphonate (DEPC)[9] under high dilution conditions to give the desired macrocycle **6**[21] in 35, 40 and 42% yields, respectively. The use of other coupling reagents[22] such as BOP, HATU, HBTU, EDCI-HOBt or EDCI-PFP led to yields lower than 10% accompanied by a complex mixture of decomposition products, including elimination compounds. Additionally, similarly disappointing results were obtained from **9** and **10** by using this set of reagents, including FDPP, DPPA or DEPC, or from **7** by the Yamaguchi procedure. The cyclic depsipeptide **6** was then subjected to catalytic hydrogenation with palladium on charcoal to give diol **26** in good yield (75%), which was monoacetylated to compound **27**.[23] This product represents an interesting analogue of stevastelin B (**2**) for biological evaluation.

In a similar synthetic sequence, epoxy aminoacid **28** was prepared and subjected to the macrolactamization reaction by the action of DEPC to furnish the epoxide analogue **29** in 40% yield. This compound represents an interesting analogue to probe the influence of the configurations at C-2 and C-3 on the immunosuppressant activity of this class of compounds. On the other hand, in order to obtain an improved yield of the epoxide **6**, we decided to synthesize it via the alkene analogue of stevastelin B followed by a final epoxidation step. Thus, the α,β-unsaturated ester **12** was subjected to a transesterification reaction mediated by dibutyltin oxide[24] to give the allyl ester **30** followed by treatment with HF·pyridine to afford the alcohol **31**. The reaction of **31** with the serine derivative **20**, in the presence of EDCI/DMAP, provided the diester **32**, which was then reacted with $Pd[PPh_3]_4$ and morpholine to give the deprotected derivative **33**. The subsequent coupling of **33** with dipeptide **23** afforded the acyclic precursor **34** in 81% yield, which was sequentially treated with Pd(0)/morpholine and TFA to furnish the seco amino acid **36**. This amino acid was subjected to the macrocyclization reaction mediated by EDCI–HOBt, to give the macrocycle **37** in 18% yield (Scheme 4). The attempted improvement of the macrocyclization yield through the use of other coupling reagents was unsuccessful. Similarly discouraging was the epoxidation of **37**, which proved to be elusive using a variety of reagents such as H_2O_2–urea and TBHP–DIPEA.[25]

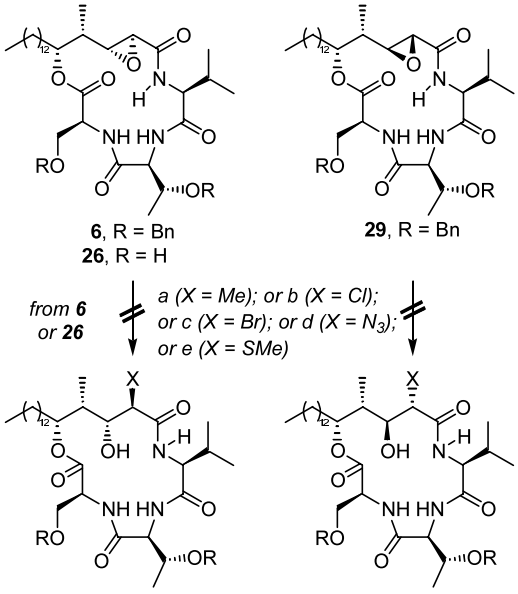
Despite the previous results, we continued the study with the epoxide **6**. Preliminary studies directed towards the synthesis of stevastelin B **2** led us to believe that the reaction of **6** with lithium dimethylcuprate would



Scheme 4. *Reagents and conditions*: (a) 2.0 equiv. DEPC, 2.0 equiv. DIPEA, DMF (2.0 mM based on **28**), 25°C, 12 h, 40%. (b) Allyl alcohol, nBu$_2$SnO, 98°C, 12 h, 99%. (c) HF·Pyr, THF, 25°C, 12 h, 99%. (d) 1.4 equiv. of **20**, 1.5 equiv. EDCI, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 2 h, 82%. (e) 0.1 equiv. $Pd(PPh_3)_4$, 5.0 equiv. morpholine, THF, 25°C, 0.5 h, 98%. (f) 1.1 equiv. of **23**, 1.5 equiv. EDCI, 1.1 equiv. HOBt, CH_2Cl_2, 25°C, 0.5 h, 81%. (g) 0.1 equiv. $Pd(PPh_3)_4$, 5.0 equiv. morpholine, THF, 25°C, 0.5 h, 96%. (h) 1. TFA, CH_2Cl_2, 25°C, 0.5 h. 2. $NaHCO_3$, Na_2CO_3, 99%. (i) 1.5 equiv. EDCI, 1.1 equiv. HOBt, CH_2Cl_2 (2.0 mM based on **36**), 0.5 h, 18%. (j) 4.0 equiv. H_2O_2, 4.0 equiv. urea, THF, 25°C, 72 h or 1.5 equiv. TBHP, 1.5 equiv. DIPEA, THF, 25°C, 72 h (starting material recovered in both cases).

provide the desired product. However, the desired ring opening reaction did not occur, giving only recovered starting material with a high degree of epimerization. In fact, reaction of **6** with different nucleophiles such as halides, azide or thiolates proved unsuccessful resulting in the recovery of starting material or the formation of a product derived from the elimination of the benzyloxy group located on the serine residue with the oxirane ring functionality intact. Consequently, we decided to test the diol **26** in reactions with different nucleophiles, including lithium dimethylcuprate, fluoride, chloride, bromide, azide and phenylthiolate, but unfortunately the same results were observed. Similarly, the action of these nucleophiles on epoxide **29** did not result in the successful formation of the desired ring-opened products (Scheme 5).

In conclusion, we have designed an approach to the [15]-membered stevastelins[26] with the aim of delivering not only the natural compounds but also analogues thereof. Initial results have proved the convergence and efficiency of our synthetic approach conducted through the epoxide **8**, which was cyclized to the desired macrocyclic derivative **6**. Initial attempts to utilize these stevastelin analogues to reach the natural members and analogues through the opening of the epoxide at C-2 with different nucleophiles proved to be elusive. Presumably, according to molecular modelling studies,[27] the preferred conformation of epoxide **6** leads to a conformational disposition of the oxirane ring that hinders the entrance and subsequent attack of nucleophiles, preventing the opening of the oxirane ring. Currently, we are considering two different strategies to overcome these important hurdles: (1) the use of catalysts capable of enhancing the reactivity of the epoxide, and (2) the nucleophilic opening of the oxirane ring prior to the key macrocyclization. Both strategies are currently being investigated and are expected to provide access to a broad family of stevastelin analogues for further biological evaluations.



Scheme 5. *Reagents and conditions*: (a) 4.0 equiv. Me_2CuLi, or Me_4AlLi, or $Me_2CuCNLi_2/BF_3$, THF, −25→0°C, 48 h. (b) 5.0 equiv. LiCl, THF/AcOH, 70°C, 72 h. (c) 5.0 equiv. LiBr, THF/AcOH, 70°C, 72 h. (d) 10.0 equiv. NaN_3, DMF/AcOH, 100°C, 72 h (starting materials recovered for a, b, c and d). (e) 2.0 equiv. MeSNa, THF, 0°C, 48 h (elimination of benzyl ether on serine residue).

Acknowledgements

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21. **Compound 6**: $R_f = 0.60$ (silica gel, hexanes:AcOEt:MeOH, 6:3:1); $[\alpha]_D^{25} = -24.4$ (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 1H, $J = 9.4$ Hz), 7.34–7.18 (m, 11H), 6.57 (d, 1H, $J = 7.0$ Hz), 5.29–5.22 (m, 1H), 4.60 (d, 1H, $J = 11.7$ Hz), 4.61–4.45 (m, 2H), 4.45 (d, 1H, $J = 11.7$ Hz), 4.40 (s, 2H), 4.11 (d, 1H, $J = 5.8$, 3.5 Hz), 3.69 (dd, 1H, $J = 9.4$, 5.3 Hz), 3.54 (dd, 1H, $J = 9.4$, 5.9 Hz), 3.31 (dd, 1H, $J = 11.2$, 7.6 Hz), 3.14 (d, 1H, $J = 2.4$ Hz), 2.97 (dd, 1H, $J = 7.6$, 2.4 Hz), 2.67–2.63 (m, 1H), 1.67–1.39 (m, 3H), 1.30–1.12 (m, 25H), 1.10 (d, 3H, $J = 7.0$ Hz), 0.97 (d, 3H, $J = 6.5$ Hz), 0.95 (d, 3H, $J = 6.5$ Hz), 0.86 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.9, 170.3, 170.2, 170.1, 137.6, 137.5, 128.5, 128.4, 127.8, 127.7, 127.6, 75.7, 73.9, 73.3, 71.0, 69.1, 66.5, 61.6, 57.7, 54.8, 53.5, 39.3, 31.9, 30.4, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.3, 27.4, 25.8, 25.4, 22.7, 19.7, 19.6, 16.2, 14.1, 11.7.
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23. **Compound 27**: $R_f = 0.59$ (silica gel, hexanes:AcOEt:MeOH, 3:6:1); ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.55 (d, 1H, $J = 8.1$ Hz), 8.51 (d, 1H, $J = 7.0$ Hz), 7.14 (d, 1H, $J = 7.5$ Hz), 4.96 (d, 1H, OH, $J = 4.8$ Hz), 4.88 (td, 1H, $J = 10.7$, 2.7 Hz), 4.38–4.31 (m, 1H), 4.28–4.18 (m, 2H), 4.13 (dd, 1H, $J = 8.1$, 3.8 Hz), 3.94–3.86 (m, 1H), 3.73 (dd, 1H, $J = 9.1$, 8.6 Hz), 3.40 (d, 1H, $J = 1.6$ Hz), 2.22–2.14 (m, 1H), 2.01–1.96 (m, 1H), 1.99 (s, 3H), 1.60–1.40 (m, 2H), 1.30–1.12 (m, 23H), 0.97 (d, 3H, $J = 6.4$ Hz), 0.94 (d, 3H, $J = 6.4$ Hz), 0.92 (d, 3H, $J = 6.4$ Hz), 0.85 (t, 3H, $J = 7.0$ Hz), 0.76 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (50.3 MHz, d_6-DMSO) δ 171.0, 170.2, 169.7, 169.1, 168.7, 77.2, 66.6, 62.8, 62.2, 57.7, 56.9, 51.1, 50.7, 35.5, 31.3, 29.0, 29.0, 28.9, 28.9, 28.7, 27.6, 25.4, 22.1, 20.6, 19.5, 19.3, 13.9, 10.2.
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26. All new compounds exhibited satisfactory spectroscopic and analytical and/or accurate mass data.
27. Theoretical calculations were performed with HyperChem 5.0, using OPLS as the force field with a gradient limit of 0.001 Kcal/(Å mol).