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# Synthetic studies toward nortriterpenoids of *schisandraceae* family. Approach to the construction of functionalized C/D and A/B ring units of micrandilactone C and rubrifloradilactone B

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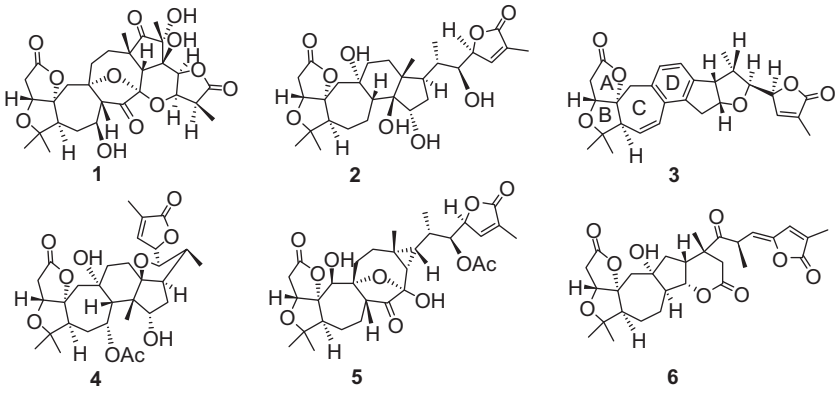
ABSTRACT

Construction of 6/7 fused bicycles featuring C/D rings of micrandilactone C and rubrifloradilactone B is reported through IMDA reaction of properly designed substrates. Also a route to the construction of a tricycle having A/B ring of nortriterpenoids of *schisandra* family is reported using RCM and a bromonium ion initiated cycloetherification reaction as the key steps.



Plants of the *Schisandraceae* family continue to be a rich source of highly bioactive nortriterpenoids.[1] Extracts of the leaves and bark of these plants are extensively used as folk medicines in China for thousands of years. Over the years a large number of compounds belonging to the family of triterpenoids with densely oxygenated novel polycyclic skeletons have been isolated from the plants of this family. Biosynthetically these compounds are proposed to be derived from cycloartane. Depending on the structural pattern, they have been classified into six different types such as schisanartane (e.g. micrandilactone A **1**), schiartane (e.g. micrandilactone C **2**), 18-nor schiartane (e.g. rubrifloradilactone B **3**), 18 (13→14)-*abeo*-schiartane (wuweizidilactone C **4**), pre-schisanartane (e.g. pre-schisanartanin A **5** and wuweiziartane (e.g. schintrilactone A **6**). Many of these compounds exhibit promising medicinal properties. For example, micrandilactone C **2**,[2] isolated from the leaves and

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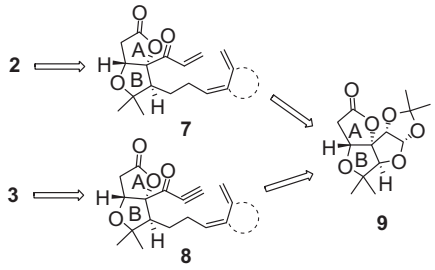


**Scheme 1.** Retrosynthesis.

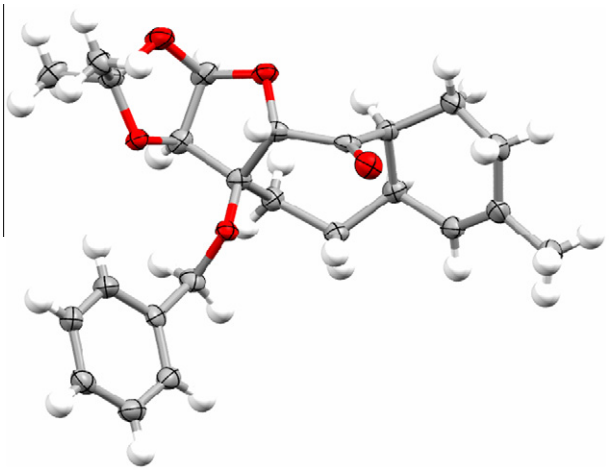


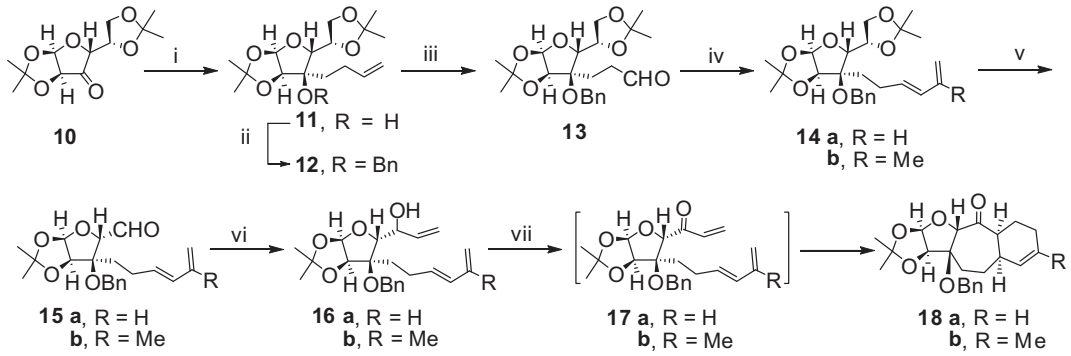
**Figure 1.** X-ray structure of compound **18b**.

stems of *Schisandra micrantha*, possesses anti-HIV activity with an $EC_{50}$ value of 7.71 μg $mL^{-1}$. Rubrifloradilactone B **3**,[3] isolated from the leaves and stems of *Schisandra Rubriflora*, exhibits anti-HIV activity with an $EC_{50}$ value of 9.75 μg $mL^{-1}$. The unique architectural features combined with the remarkable medicinal properties, *schisandra* terpenoids have elicited considerable interest[4] among synthetic organic chemists. Examination of the structures reveals the presence of the A/B/C ring as the common structural unit. Thus synthetic efforts have so far remained restricted to the development of strategies for the construction of A/B[4j,k,d] or A/B/C[4b,g,l,n] fragments. There are also few reports on the construction of the central carbocyclic[4a,e,f,h,i,m,o] core of some of these compounds. However there is no report aimed at the synthesis of micrandilactone C **2**, and there is only a single report[5] on the construction of a tricyclic core structure of rubrifloradilactones.

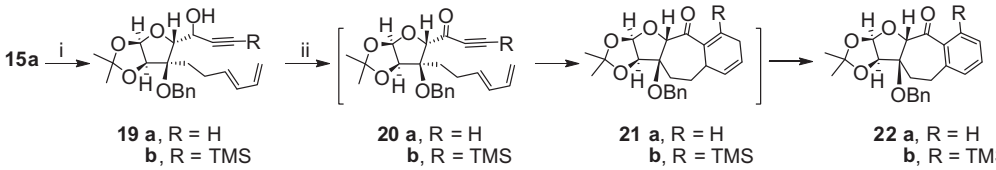
Remarkable inhibitory activity of these two terpenoids against HIV-1 replication stimulated our interest in developing routes to the total synthesis of these natural products. We initially embarked on developing a flexible route that could be employed to construct functionalized tetracyclic A/B/C/D fragments present in both **2** and **3**. Retrosynthetically, an intramolecular Diels–Alder (IMDA) reaction in an appropriately designed substrate having the diene–dienophilic component stitched together through the pre-built A/B ring was envisaged as the key step (Scheme 1). To this end an IMDA reaction in **7** was considered for the construction of the C/D ring present in **2** while an IMDA reaction in **8** having a conjugated acetylenic ketone as the dienophilic component could be employed for the synthesis of the C/D ring aromatic analogue present in **3**. Precursors **7** and **8** could in principle be available from **9**. Herein we report the preliminary results of our investigation on IMDA reaction for the construction of C/D rings of **2** and **3** and a route to the synthesis of the projected intermediate **9** featuring A/B ring present in a large number of *schisandra* nortriterpenoids.

We initially focussed on determining the feasibility of the IMDA reaction to construct 6/7 fused ring system as it is present in a large number of terpenes other than *schisandra* nortriterpenes. Intramolecular Diels–Alder reaction has been extensively explored to construct hydrindane and decalin systems. However, there are only few reports[6] on IMDA reactions of undecatrienones to produce 6/7 fused bicycles due to their significantly reduced reactivity toward cycloaddition. Successful construction of 6/7 fused rings[7] by IMDA reaction requires high temperature,[7a–c] long reaction time[7d] and even in some cases high pressure.[8] During this investigation we observed that intramolecular Diels–Alder reaction of the undecatrienones **17** and **20** in which the dienes and the dienophiles were tethered through a furanosugar unit is very facile.

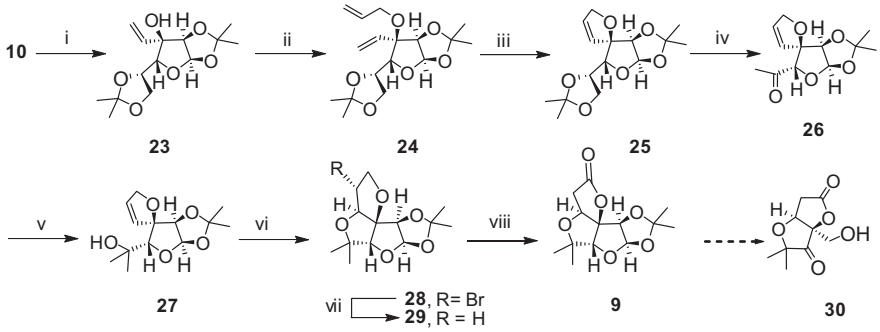
The precursor **17a** for the IMDA reaction was prepared as delineated in Scheme 2. Reaction of the glucose derivative **10** with the Grignard reagent prepared from 4-bromo-1-butene led to the known carbinol **11**[9] in 50% isolable yield. Protection of the hydroxyl group as benzyl ether **12** followed by cleavage of the terminal alkene unit produced the aldehyde **13** in over all excellent yield. The aldehyde **13**[10] was then subjected to Wittig reaction with the ylide generated from allyl triphenylphosphonium bromide to produce the diene **14a** in good yield. Selective deprotection of the 5,6-acetonide moiety followed by periodate cleavage of the resulting vicinal diol provided the aldehyde **15a**. Addition of vinyl magnesium bromide to the aldehyde **15a** produced the carbinol **16a**. When the carbinol **16a** was subjected to Dess–Martin periodinane (DMP) oxidation at rt, to our delight the tricyclic ketone **18a**




**Scheme 2.** Reagents and conditions: (i) 4-Bromo-1-butene, Mg, $Et_2O$, 0 °C, 2 h, 50%; (ii) NaH, THF, 0 °C, HMPA, BnBr, 4 h, 95%; (iii) $OsO_4$, THF–$H_2O$ (3:2), $NaIO_4$, 0 °C, 12 h, 80%; (iv) (a) $^n$BuLi, allyltriphenylphosphonium bromide, THF, 0 °C, 1 h, 62%; (b) $^n$BuLi, (2-methyl-2-propenyl)triphenylphosphonium bromide, THF, 0 °C, 1 h, 60%; (v) (a) 70% aq AcOH, rt, 12 h, 80% (R = H) and 70% (R = Me); (b) $NaIO_4$, THF–$H_2O$ (3:2), 0 °C, 2 h, 75% (R = H) and 70% (R = Me); (vi) $CH_2$–CHMgBr, THF, −78 °C to rt, 55% (R = H) and 60% (R = Me); (vii) DMP, $CH_2Cl_2$, 0 °C to rt, 9 h, 85% (R = H) and 80% (R = Me).




**Scheme 3.** Reagents and conditions: (i) (a) Ethynylmagnesium bromide, THF, −78 °C to rt, 60%; (b) ethynyltrimethylsilane, $^{n}$BuLi, THF, −78 °C to rt, 65%; (ii) DMP, $CH_2Cl_2$, 0 °C to rt, 9 h, 45% (R = H) and 50% (R = TMS).




**Scheme 4.** Reagents and conditions: (i) $CH_2$=CHMgBr, THF, −78 °C to rt, 2 h, 80%; (ii) NaH, $CH_2$=$CHCH_2Br$, THF, rt, 92%; (iii) [$(PCy_3)_2Cl_2Ru$=CHPh], $CH_2Cl_2$, rt, 6 h, 95%; (iv) (a) 60% aq AcOH, rt, 12 h, 88%; (b) $NaIO_4$, MeOH–$H_2O$ (2:1), 0.5 h, 84%; (c) MeMgI, $Et_2O$; (d) DMP, $CH_2Cl_2$, 68% (two steps); (v) MeMgI, $Et_2O$, 0 °C, 1 h, 80%; (vi) NBS, DMF, rt, 1 h, 95%; (vii) TBTH, AIBN, toluene, reflux, 2 h, 90%; (viii) $RuCl_3$, $NaIO_4$, rt, 5 h, 75%.

was obtained directly in excellent yield through IMDA reaction of the in situ generated trienone **17a**.

Intrigued by facile IMDA reaction of **17a** during its generation, we extended this protocol to make **18b**. The aldehyde **13** was treated with the ylide generated from (2-methyl-2-propenyl) triphenylphosphonium bromide to produce the diene **14b**. The diene **14b** was then transformed to the carbinol **16b** following the protocol described for the transformation of **14a** to **16a**. Treatment of **16b** with DMP at rt similarly produced the tricyclic ketone **18b** arising through facile IMDA reaction of the in situ generated trienone **17b**. The structure of the adduct **18b** was determined through X-ray (Fig. 1).[11] This led to assignment of structure to the adduct **18a**. The facile intramolecular Diels–Alder reaction of **17a** and **17b** to form fused 6/7 bicyclic systems prompted us to examine the reactivity with acetylenic dienophiles in order to make benzosuberone derivatives present in rubrifloradilactone B **3**. Toward this direction the aldehyde **15a** was allowed to react with ethynylmagnesium bromide to produce the carbinol **19a** in excellent yield. Attempted oxidation of this carbinol with DMP led directly to the benzosuberone derivative **22a** in overall very good yield through IMDA reaction of the in situ generated ketone **20a** to the diene **21a** (could not be isolated) followed by its in situ dehydrogenation. It may be noted that aromatization of 3,6-cyclohexadiene generally requires[7b] treatment with DDQ. In the present case it occurred spontaneously. In a similar fashion, the trimethyl silylated benzosuberone derivative **22b** was obtained as delineated in Scheme 3. Thus by using IMDA reaction, C/D fused ring present in micrandilactone C and rubrifloradilactone B can be made. The facile IMDA reaction observed above suggests that appropriately constructed undecatrienones on a prebuilt A/B ring can provide the A/B/C/D rings present in **1** and **2**.

After successfully demonstrating the feasibility of IMDA reaction to construct 6/7 bicyclic system, we next focused on the construction of the ring system **9** featuring the A/B ring of the *schisandra* terpenoids. Reaction of the ketone **10**[12] with vinylmagnesium bromide produced the known carbinol **23** in excellent yield. The carbinol was then transformed to the allyl ether **24** in 92% yield. Ring closing metathesis (RCM)[13] of the diene **24** with

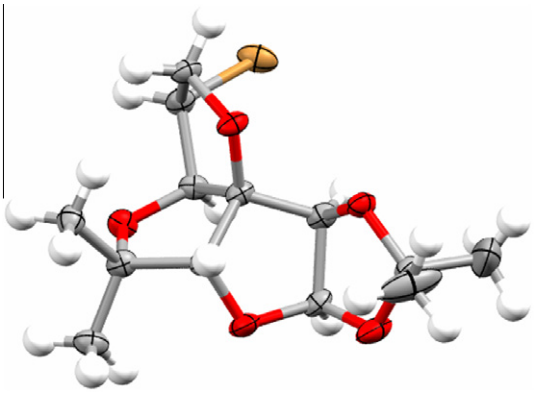


**Figure 2.** X-ray structure of compound **28**.

Grubbs' 1st generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] afforded the dihydrofuran derivative **25** in near quantitative yield. The dihydrofuran derivative **25** was then converted to the methyl ketone **26** as delineated in Scheme 4 in over all good yield. Addition of methylmagnesium iodide to **26** afforded the carbinol **27**. The dihydrofuran derivative **27** when treated with NBS-DMF underwent smooth bromonium ion initiated cycloetherification to produce the tricyclic bromide **28** in 95% yield. The structure of this compound was established through X-ray (Fig. 2). Reductive elimination of bromine from **28** was achieved on treatment with tributyltin hydride (TBTH) to afford the tricycle **29**. The tricycle **29** was then smoothly converted to the lactone **9** on oxidation with $RuCl_3$–$NaIO_4$. The sugar residue in the lactone **9** can in principle be elaborated to IMDA precursor analogous to **17** and **20** through the keto-lactone **30** for annulation of the C/D rings toward the synthesis of the nortriterpenoids **2** and **3**.

In conclusion, we have developed an IMDA reaction based route to construct fused 6/7 bicycle featuring C/D ring systems present in the nortriterpenoids **2** and **3**. We have also developed a route for the construction of the A/B ring present in *schisandra* terpenoids

using RCM and a bromonium ion initiated cycloetherification reactions as the key steps.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.104.

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10. All new compounds were characterized on the basis of IR, $^1$H, $^{13}$C NMR and HRMS data. Spectral data for selected compounds: Compound **18a**. Mp 124–125 °C; $[\alpha]_D^{24}$ −48.41 (*c* 1.5, $CHCl_3$); IR $\nu_{max}$ (liquid film) 1711 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36–7.18 (5H, m), 5.88 (1H, d, *J* = 3.5 Hz), 5.71 (1H, ddd, *J* = 10.0, 6.3, 3.8 Hz), 5.30 (1H, dd, *J* = 10.0, 2.2 Hz), 4.58 (1H, d, *J* = 10.8 Hz), 4.48 (1H, d, *J* = 12.2 Hz), 4.46 (1H, br s), 4.29 (1H, d, *J* = 3.5 Hz), 3.42–3.31 (1H, m), 2.47–2.33 (2H, m), 2.08 (1H, dd, *J* = 12.3, 8.0 Hz), 1.91–1.85 (1H, m), 1.73–1.52 (3H, m), 1.51(3H, s), 1.47–1.34 (2H, m), 1.30 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 209.4 (CO), 138.4 (C), 128.6 (CH), 128.3 (2CH), 127.8 (CH), 127.6 (CH), 127.5 (2CH), 113.9 (C), 105.4 (OCHO), 86.6 (OCH), 84.2 (C), 83.5 (OCH), 66.6 ($OCH_2$), 41.9 (CH), 34.8 (CH), 30.1 ($CH_2$), 27.1 ($CH_3$), 29.0 ($CH_3$), 26.2 ($CH_2$), 23.0 ($CH_2$), 21.5 ($CH_2$); HRMS (ESI) calcd for $C_{23}H_{28}O_5Na$ $(M+Na)^+$, 407.1834; found, 407.1834. Compound **18b**. Mp 137–138 °C; $[\alpha]_D^{26}$ −26.48 (*c* 0.33, $CHCl_3$); IR $\nu_{max}$ (liquid film) 1715 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45–7.29 (5H, m), 5.9 (1H, d, *J* = 3.6 Hz),5.08 (1H, s), 4.65 (1H, d, *J* = 10.8 Hz), 4.53 (1H, d, *J* = 10.7 Hz), 4.52 (1H, s), 4.36 (1H, d, *J* = 3.5 Hz), 3.39–3.33 (1H, m), 2.51 (1H, m), 2.35–2.31 (1H, m), 2.17–2.10 (2H, m), 1.87–1.70 (3H, m), 1.67 (3H, s), 1.59 (3H, s), 1.53–1.41 (1H, m), 1.37 (3H, s), 1.32–1.26 (1H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 209.4 (CO), 138.4 (C), 135.0 (C), 128.4 (CH), 128.3 (CH), 127.6 (2CH), 127.5 (CH), 122.9 (CH), 113.9 (C), 105.5 (OCHO), 86.8 (OCH), 84.5 (C), 83.5 (OCH), 66.6 ($OCH_2$), 41.6 (CH), 35.3 (CH), 30.1 ($CH_2$), 27.9 ($CH_3$), 27.1 ($CH_3$), 27.0 ($CH_3$), 26.4 ($CH_2$), 23.9 ($CH_2$), 22.1 ($CH_2$); HRMS (ESI) calcd for $C_{24}H_{30}O_5Na$ $(M+Na)^+$, 421.1991; found, 421.1992. Compound **22a**. Mp 197–198 °C; $[\alpha]_D^{26}$ −15.7 (*c* 0.59, $CHCl_3$); IR $\nu_{max}$ (liquid film) 1697 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60 (1H, d, *J* = 7.5 Hz), 7.41–7.24 (7H, m), 7.17 (1H, d, *J* = 7.5 Hz), 5.98 (1H, d, *J* = 3.8 Hz), 4.84 (1H, br s), 4.76 (1H, d, *J* = 10.9 Hz), 4.67 (1H, d, *J* = 10.9 Hz), 4.57 (1H, d, *J* = 3.84 Hz), 3.16–3.08 (1H, m), 2.92–2.83 (1H, m), 2.33–2.18 (2H, m), 1.63 (3H, s), 1.39 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.1 (CO), 140.5 (C), 138.4 (C), 136.8 (C), 131.6 (CH), 129.6 (CH), 129.4 (CH), 128.3 (2CH), 127.6 (2CH), 127.3 (CH), 126.8 (CH), 113.7 (C), 106.2 (OCHO), 88.3 (OCH), 85.7 (C), 83.8 (OCH), 67.1 ($CH_2$), 32.7 ($CH_2$), 29.0 ($CH_2$), 27.1 ($CH_3$), 26.9 ($CH_3$); HRMS (ESI) calcd for $C_{23}H_{24}O_5Na$ $(M+Na)^+$, 403.1521; found, 403.1524. Compound **22b**. $[\alpha]_D^{26}$ 56.0 (*c* 3.5, $CHCl_3$); IR $\nu_{max}$ (liquid film) 1680 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (1H, d, *J*= 7.5 Hz), 7.40–7.23 (6H, m), 7.09 (1H, d, *J* = 7.5 Hz), 5.83 (1H, d, *J* = 3.6 Hz),4.78 (1H, d, *J* = 10.2 Hz), 4.76 (1H, s), 4.69 (1H, d, *J* = 10.2 Hz), 4.39 (1H, d, *J* = 3.6 Hz), 3.10 (1H, dd, *J* = 15.6, 10.5 Hz), 2.61 (1H, dd, *J* = 15.8, 8.8 Hz), 2.26 (1H, dd, *J* = 14.8, 8.8 Hz), 1.85 (1H, dd, *J* = 14.2, 11.2 Hz), 1.61 (3H, s), 1.33 (3H, s), 0.27 (9H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 206.5 (CO), 144.5 (C), 140.2 (C),138.4 (C), 136.8 (C), 133.5 (CH), 129.5 (CH), 129.4 (CH), 128. (CH), 128.4 (CH), 127.5 (3CH), 113.6 (C), 105.6 (OCH), 86.3 (C), 85.9 (OCH), 83.1 (OCH), 67.0 ($OCH_2$), 30.4 ($CH_2$), 28.7 ($CH_2$), 26.9 ($2CH_3$), 0.47 ($3CH_3$); HRMS (ESI) calcd for $C_{26}H_{32}O_5SiNa$ $(M+Na)^+$, 475.1917; found, 475.1917. Compound **25**. $[\alpha]_D^{27}$ 68.7 (*c* 1.8, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.14 (1H, d, *J* = 6.3 Hz), 5.74 (1H, d, *J* = 3.5 Hz), 5.70 (1H, dt, *J* = 6.3, 2.3 Hz), 4.71 (2H, t, *J* = 2.1 Hz), 4.24 (1H, d, *J* = 3.5 Hz), 4.14 (1H, d, *J* = 6.6 Hz), 3.98–3.89 (3H, m), 1.60 (3H, s), 1.40 (3H, s), 1.33 (3H, s), 1.28 (3H, s); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 130.8 (CH), 124.9 (CH), 113.3 (C), 109.3 (C), 103.2 (CH), 95.9 (C), 83.2 (CH), 79.3 (CH), 75.9 ($CH_2$), 74.4 ($CH_2$), 67.0 ($CH_2$), 27.0 ($CH_3$), 26.7 ($CH_3$), 26.4 ($CH_3$), 25.6 ($CH_3$); HRMS (ESI) calcd for $C_{15}H_{22}O_6Na$ $(M+Na)^+$, 321.1314; found, 321.1314. Compound **9**. $[\alpha]_D^{26}$ 65.1 (*c* 0.53, $CHCl_3$); IR (liquid film) $\nu_{max}$ 1784 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.97 (1H, d, *J* = 3.5 Hz), 4.51 (1H, d, *J* = 6.5 Hz), 4.49 (1H, d, *J* = 3.6 Hz), 4.46 (1H, s), 2.75 (2H, m), 1.61 (3H, s), 1.37 (3H, s), 1.31 (3H, s), 1.26 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.0 (CO), 114.3 (C), 105.3 (CH), 98.9 (C), 87.0 (CH), 86.0 (CH), 79.9 (CH), 78.5 (CH), 36.9 ($CH_2$), 27.2 ($2CH_3$), 27.0 ($CH_3$), 23.2 ($CH_3$); HRMS (ESI) calcd for $C_{13}H_{18}O_6Na$ $(M+Na)^+$, 293.1001; found, 293.1005.
11. Crystal data: Compound **18b**. Colorless block shaped crystal (0.32 × 0.27 × 0.14 mm) of **18b** was analyzed. Empirical formula $C_{24}H_{30}O_5$, *Mr* = 398.48, orthorhombic space group $P2_12_12_1$ (No. 19), *a* = 5.6717(7), *b* = 12.6924(16), *c* = 28.958(4) Å, *V* = 2084.6(4) Å$^3$, *T* = 100 K, *Z* = 4. $\rho_{calcd}$ = 1.270 g cm$^{-3}$. *F*(000) = 856, $\lambda$(Mo-K$\alpha$) = 0.71073 Å, $\mu$ Mo K$\alpha$/mm$^{-1}$ = 0.088, $2\theta_{max}$ = 50.0°, 19771 total reflections, 3672 unique reflections, 3428 observed ($I > 2\sigma(I)$) 265 parameters; $R_{int}$ = 0.0332, $R_1$ = 0.0317; $wR_2$ = 0.0790 ($I > 2\sigma(I)$), $R_1$ = 0.0346; $wR_2$ = 0.0813 (all data) with GOF = 1.025. Compound **28**. $C_{13}H_{19}BrO_5$, *M* = 335.19, orthorhombic, space group $P2_12_12_1$, *a* = 5.6969(5), *b* = 10.2560(9), *c* = 24.299(2) Å, *V* = 1419.7(2) Å$^3$, *T* = 298 K, *Z* = 4. *F*(000) = 688, $\mu$ = 2.909 mm$^{-1}$, $2\theta_{max}$ = 49.98°, 13110 reflections were collected, 2345 observed ($I > 2\sigma(I)$) 176 parameters; $R_{int}$ = 0.0287, $R_1$ = 0.0254; $wR_2$ = 0.0608 ($I > 2\sigma(I)$), $R_1$ = 0.0288; $wR_2$ = 0.0622 (all data) with GOF = 1.014. X-ray single crystal data were collected using MoK$\alpha$ ($\lambda$ = 0.7107 Å) radiation on a SMART APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. The structures were solved by direct method and refined in a routine manner. Non hydrogen atoms were treated anisotropically. The hydrogen atoms were geometrically fixed. CCDC (CCDC Nos. 830899 for **18b** and 835934 for **28**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk.
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