

Ru–Ru bonds. Although the structural properties for **4a** are also common to the clusters **6** and **7**, the bond lengths of **6** and **7** are slightly elongated, probably due to the increased steric repulsion among the C_5R_5 ($R = H$ or Me) ligands. The mean values of the distance between a ruthenium center and the centroid of the affiliated $\eta^5-C_5H_5$ (Cp) ring are in the order of **4a** > **6** > **7**. This result suggests that the increase in electron density at the metal centers arising from the introduction of methyl groups into the Cp ring enhances the back donation from the ruthenium center to the Cp group.

We have developed the first rational synthesis of a series of tetranuclear polyhydride complexes containing several different combinations of auxiliary cyclopentadienyl ligands and demonstrated that the electron density at the metal centers and the size of the reaction site of the tetranuclear cluster complex is most probably controllable by changing the number of methyl groups on the C_5 rings.

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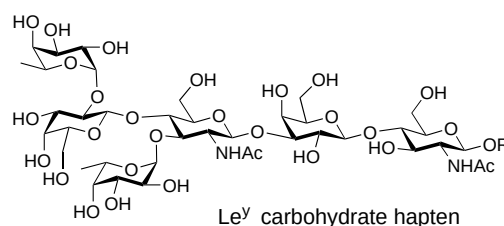
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crystal data: monoclinic, $P2_1/n$, $a = 18.217(5)$, $b = 16.475(9)$, $c = 9.772(6)$ Å, $\beta = 90.87(3)^{\circ}$, $V = 2932(3)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.837$ g cm⁻³; 8976 reflections ($6^{\circ} \leq 2\theta \leq 55^{\circ}$), 5691 observed with $F > 2\sigma(F)$, 282 parameters; $R_1 = 0.039$, $wR_2 = 0.108$. X-ray structure analysis for **7**: Measurement performed on an AFC-7R four-circle diffractometer at $-80^{\circ}C$; crystal data: monoclinic, $P2_1/a$, $a = 24.026(3)$, $b = 16.699(2)$, $c = 17.388(3)$ Å, $\beta = 90.37(1)^{\circ}$, $V = 6955(1)$ Å³, $Z = 8$, $\rho_{\text{calcd}} = 1.683$ g cm⁻³; 16893 reflections ($5^{\circ} \leq 2\theta \leq 60^{\circ}$), 10387 observed with $F > 3\sigma(F)$, 703 parameters; $R = 0.039$, $R_w = 0.043$. CCDC-177793 (**4a**), CCDC-177794 (**4b**), CCDC-177795 (**4c**), CCDC-177796 (**6**), and CCDC-177797 (**7**) 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).

Reactivity-Based One-Pot Synthesis of a Lewis Y Carbohydrate Hapten: A Colon–Rectal Cancer Antigen Determinant**

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Lewis Y (Le^y) is part of a type 2 blood group antigen that carries a carbohydrate hapten containing two α -linked fucosyl moieties, one at the C-2 hydroxy group of the terminal galactose and the other at the C-3 hydroxy group of subterminal *N*-acetylglucosamine (Scheme 1).^[1] As a tumor-



Scheme 1. The structure of a Le^y carbohydrate hapten.

related glycoconjugate, it is expressed on the tumor cell surface in 96 % of colon–rectal adenocarcinoma and 46 % of hepatocellular carcinoma.^[2] Therefore, it is important to understand its pathological roles and to explore its antigenic properties to allow the development of cancer diagnostic and immunotherapeutic agents.^[3] Recently, the Le^y hapten has been synthesized by Danishefsky's group as part of a multi-antigenic glycopeptide to exploit its potential as a carbohydrate-based anticancer vaccine.^[4]

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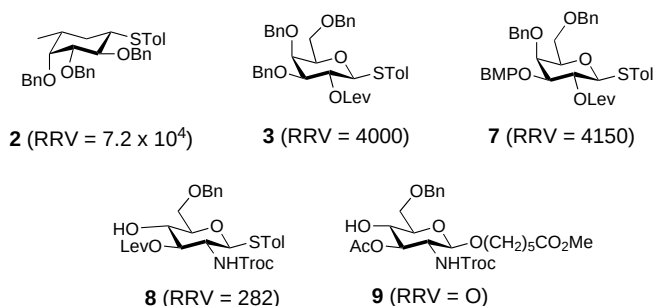
Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

The first synthesis of the Le^y hapten by Sinaÿ and Jacquinet involved the use of glycosyl orthoester and bromide donors.^[5] Schmidt et al. and Danishefsky et al. developed new syntheses using trichloroacetimidate and glycal methodologies.^[6] As part of our effort to develop automated programmable one-pot oligosaccharide synthesis without manipulation of protecting groups, we report here the design of building blocks with appropriate reactivity for use in the one-pot synthesis of the Le^y hapten.^[7,8] The special feature of this work lies in the integration of four glycosylation steps into one synthetic operation to furnish the target oligosaccharide in a few hours without any need for protecting group manipulation and intermediate isolation.

Reactivity-based one-pot synthesis is a newly developed strategy aimed at simplification of the complex synthetic procedures needed for oligosaccharide synthesis. It relies on the design, synthesis, and reactivity measurements of a large pool of thioglycoside building blocks to create a reactivity database. Based on this database and simple chemistry logic or computer software called "OptiMer",^[7] an appropriate combination of thioglycoside building blocks can be derived for any given oligosaccharide structure, and these building blocks can be used for the one-pot synthesis.

Retrosynthetic analysis of Le^y divided the hapten into three tentative units: a fucosyl, a dihydroxy bridging lactosaminyl, and a reducing end lactosaminyl unit (Scheme 2). To charge these units with different reactivity, different protecting groups were used based on the information derived from our current reactivity database.^[9] Simultaneously, orthogonal protection groups were required to provide potential acceptor sites for later glycosylation. Bearing this in mind, three functional building units **2**, **11**, and **13** were designed and synthesized. After consulting the reactivity database, a perbenzylated fucosyl thioglycoside was identified as our functional fucosyl donor **2** due to its high relative reactivity

value ($RRV = 7.2 \times 10^4$) and its preparation followed the literature procedure.^[7] The bridging lactosaminyl unit was prepared from the corresponding galactosyl unit **3** and glucosaminyl unit **8**, while the reducing end lactosaminyl units was synthesized from the galactosyl unit **7** and the glucosaminyl unit **9** (Scheme 3).

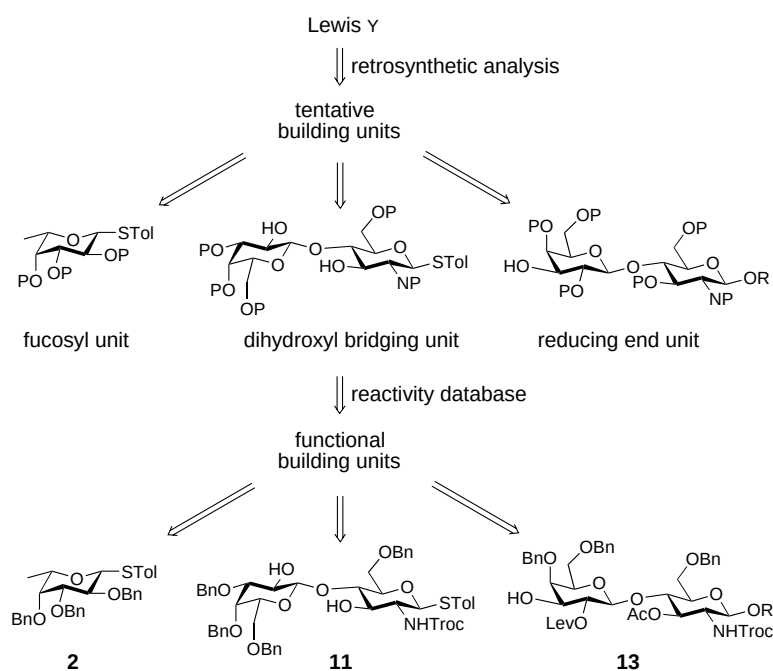


Scheme 3. Relative reactivity values (RRV) of functional building units **2**, **3**, and **7–9**.

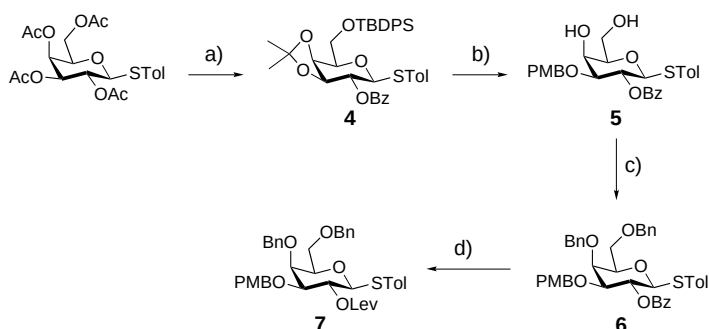
Building block **8** was chosen as the reducing end component of the bridging building block **11** because the reactivity of **11** was expected to be close to that of **8** based on the results of our previous study and should be an optimal building unit for coupling with the first donor **2** ($RRV = 7.2 \times 10^4$) in the planned one-pot operation.^[7] Galactosyl thioglycoside **3** was prepared according to the literature procedure reported by Sinaÿ and Jacquinet.^[4] Synthesis of galactosyl **7** began with the peracetylated β -galactosyl thioglycoside^[7] that was deacetylated under Zemplén conditions (Scheme 4). The resulting deacetylated product was silylated at the C-6 hydroxy group with *tert*-butyldiphenylsilyl chloride (TBDPSCI). Isopropylidenation with 2,2-dimethoxypropane masked the C-3 and C-4 hydroxy groups, and the remaining

C-2 hydroxy group was benzoylated with benzoyl chloride (BzCl) to furnish the fully protected compound **4**. The isopropylidene acetal function of **4** was removed with 70% acetic acid at 80 °C, and the deprotected product was selectively benzylated with *p*-methoxybenzyl chloride (PMBCl) at the C-3 hydroxy group in the presence of dibutyltin(II) oxide. Removal of the TBDPS protecting group at the C-6 hydroxy group then furnished compound **5**. Subsequent benzylation of the C-4 and C-6 hydroxy groups with benzyl bromide (BnBr) gave compound **6**. Previous work showed that removal of benzoate group was sometimes problematic^[10] and so it was replaced with levulinoate to give **7** by consecutive debenzoylation and levulinoylation by using Zemplén deacylation and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) mediated levulinoylation, respectively. Syntheses of glucosaminyl units **8** and **9** were straightforward with standard operations.

With the prepared monosaccharide building blocks **2**, **3**, **7**, **8** and **9** in hand, their RRVs were obtained by HPLC analysis with the established competitive assay method (see Scheme 3).^[7] Under

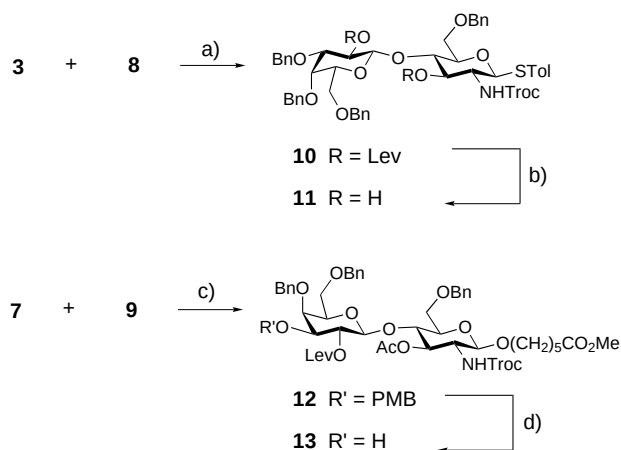


Scheme 2. Retrosynthetic analysis for one-pot synthesis of the Le^y hapten.



Scheme 4. Synthesis of galactosyl building unit **7**. a) 1) NaOMe, MeOH/CH₂Cl₂; 2) TBDPSCl, imidazole, DMF; 3) 2,2-dimethoxypropane, cat. CSA, acetone; 4) BzCl, pyridine, CH₂Cl₂, 54% for four steps; b) 1) 70% AcOH in H₂O, 80°C; 2) Bu₂SnO, benzene/toluene, 120°C, 18 h; 3) *p*-methoxybenzyl chloride, cat. Bu₄NI, toluene, 90°C, 6 h; 4) TBAF, THF, 60% for four steps; c) BnBr, NaH, cat. Bu₄NI, DMF, 90%; d) 2) NaOMe, MeOH/CH₂Cl₂; 2) levulinic acid, EDC, DMAP, 90% for two steps. Lev = levulinoyl, Tol = *p*-methylphenyl, CSA = camphorsulfonic acid, DMAP = dimethylaminopyridine.

the guidance of these RRVs, the bridging and reducing end lactosaminyl building units were synthesized (Scheme 5). Galactosyl donor **3** (RRV = 4000) was glycosylated with

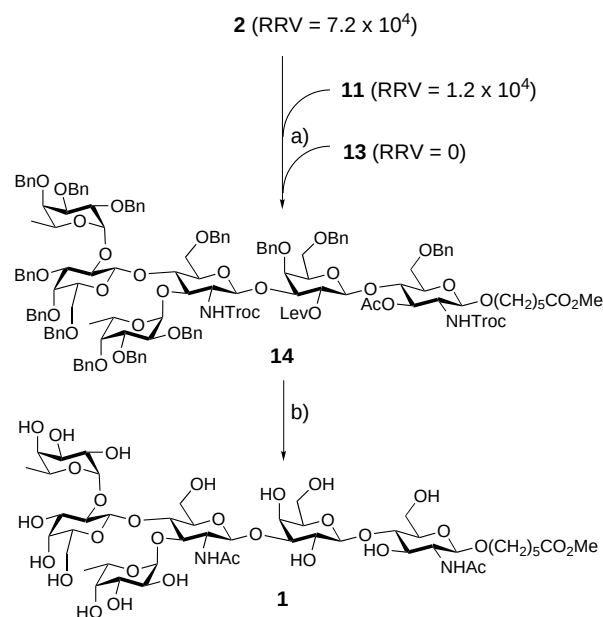


Scheme 5. Synthesis of lactosaminyl building units **10–13**. a) NIS, cat. TfOH, MS (AW300), –45°C, 40%; b) 4M NH₂NH₂·xH₂O in AcOH/pyridine, pyridine, 80%; c) NIS, cat. TfOH, MS (AW300), –45°C, 70%; d) DDQ, CH₂Cl₂/phosphate buffer, 70%. Troc = 2,2,2-trichloroethoxycarbonyl.

glucosaminyl acceptor **8** (RRV = 282) in the presence of *N*-iodosuccinimide/triflic acid (NIS/TfOH) to yield the precursor of the bridging lactosaminyl unit **10** in 40% yield.^[11] Deprotection of the two levulinoate groups with hydrazine hydrate in an acetic acid/pyridine (3:2) mixture converted **10** into the functional bridging unit **11** in 80% yield.^[12] The reducing end lactosaminyl unit precursor **12** was prepared in 70% yield by glycosylation of the galactosyl donor **7** with glucosaminyl acceptor **9** in the presence of NIS/TfOH. Cleavage of the PMB protecting group with dichlorodicyanoquinone (DDQ) furnished the functional reducing end lactosaminyl unit **13**. Unexpectedly, the RRV of **11** was determined to be 1.2×10^4 , which was 43-fold greater than its constituted glucosaminyl unit **8** (RRV = 282).^[7] The differ-

ence was probably due to the removal of two electron-withdrawing protecting groups (Lev) and hence increased the reactivity of the resulting thioglycoside building block. For the reducing end lactosaminyl unit **13**, a zero reactivity value was assigned.

The RRVs of all the functional building units, **2** (RRV = 7.2×10^4), **11** (RRV = 1.2×10^4), **13** (RRV = 0), presented an appropriate reactivity profile for one-pot synthesis. The one-pot synthetic operation was performed in the presence of the NIS/TfOH promotor system (Scheme 6). The first glycosylation between the fucosyl donor **2** and the functional bridging



Scheme 6. One-pot synthesis of the Le^y hapten **14** and its deprotected compound **1**. a) 1) NIS, cat. TfOH, MS (AW300), –70°C; 2) **13**, NIS, cat. TfOH, –25°C, 44%; b) 1) Zn dust, Ac₂O; 2) NaOMe, MeOH/CH₂Cl₂; 3) Pd-black, H₂, MeOH/AcOH, 25% for three steps. NHAc = *N*-acetamido.

lactosaminyl unit **11** was performed at –70°C, whereas the second glycosylation required higher temperature (–25°C). The lower temperature for the first glycosylation suppressed the formation of undesired succinimide by-product. In addition, low temperature favors the formation of the α -glycosidic linkage.^[13] The second glycosylation involves the coupling of two large sugar fragments for which a higher temperature was necessary for a practical reaction. The yield of fully protected determinant **14** was 44%, which was equivalent to 81% per glycosylation. Global deprotection of **14** was performed in three steps. Zinc dust in acetic anhydride removed the two trichloroethyl carbamate protecting functions (Troc) on **14** and reacylated the free amino groups simultaneously. The remaining levulinoate and acetyl protecting functions were cleaved by Zemplén deacylation. The final debenzilation was accomplished by way of a palladium-black catalyzed hydrogenation. Target Le^y hapten (**1**) was obtained in 25% yield from **14**. The characterization and anomeric purity of **1** were confirmed by HRMS and NMR analysis.

In conclusion, we have demonstrated the application of a reactivity-based one-pot strategy for the synthesis of the tumor-related oligosaccharide, Lewis Y hapten. The strategy

incorporates four glycosylation reactions into one synthetic operation, which significantly reduces the operation time to a few hours and improves the efficiency of the entire synthetic process. The building blocks (**3**, **7**, **8**, **11**) and their relative reactivity values have been proven to be useful for glycosylations as demonstrated in this study. These building blocks have been added to the OptiMer database (currently containing ~300 building blocks) and should find use in the programmable synthesis of Le^y and other oligosaccharides.

Experimental Section

Reactivity-based one-pot synthesis of the Le^y hapten **14**: Perbenzylated β -fucosyl thioglycoside donor **2** (0.31 g, 0.58 mmol), dihydroxyl lactosaminyl unit **11** (0.25 g, 0.25 mmol), and activated molecular sieves (AW300) were suspended in CH₂Cl₂ (6 mL) under argon and stirred for 1 h at room temperature. The reaction mixture was then cooled to -70 °C, and NIS (0.13 g, 0.58 mmol) and 0.5 M TfOH in diethyl ether (80 μ L, 0.04 mmol) were added. The reaction was monitored by thin layer chromatography (TLC) (hexane/CH₂Cl₂/EtOAc, 3:1:0.5). After complete consumption of **2**, reducing end lactosaminyl unit **13** (0.39 g, 0.37 mmol), a second portion of NIS (0.083 mg, 0.37 mmol), and 0.5 M TfOH in diethyl ether (40 μ L, 0.02 mmol) were added to the reaction mixture. The reaction temperature was raised to -25 °C and the reaction was monitored by TLC (hexane/EtOAc, 3:2). The reaction was quenched with addition of saturated sodium bicarbonate (sat. NaHCO₃) and solid sodium thiosulfate (Na₂S₂O₃). Molecular sieves were then filtered off and the filtrate was washed with saturated Na₂S₂O₃, saturated NaHCO₃, and brine, and dried (MgSO₄). The concentrate was purified with flash column chromatography (toluene/CH₂Cl₂/EtOAc, 4:1:1) to give **14** (0.3 g, 44%) as glassy white solid. ¹H NMR (600 MHz, CDCl₃, 20 °C): δ = 1.12 (d, *J* = 6.6 Hz, 3H; fucosyl-CH₃), 1.24 (d, *J* = 6.6 Hz, 3H; fucosyl-CH₃), 1.34 (t, *J* = 7.5 Hz, 2H; aglycon-CH₂), 1.54–1.60 (m, 4H; aglycon-CH₂), 1.85 (s, 3H; CH₃C=O), 2.09 (s, 3H; CH₃C=O), 2.28 (dt, *J* = 7.5, 2.2 Hz, 2H; aglycon-CH₂), 2.34 (d, *J* = 18 Hz, 1H; lev-CH₂), 2.43 (d, *J* = 19 Hz, 1H; lev-CH₂), 2.63 (br, 1H; lev-CH₂), 2.79 (dd, *J* = 18, 8.0 Hz, 1H; lev-CH₂), 3.15 (br, 1H), 3.31–3.34 (m, 2H), 3.41–3.52 (m, 5H), 3.55–3.60 (m, 3H), 3.65 (s, 3H), 3.67–3.71 (m, 6H), 3.81–3.93 (m, 7H), 3.97 (br, 2H), 4.04–4.10 (m, 3H), 4.17 (br, 1H), 4.28–4.81 (m, 34H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.99–5.05 (m, 3H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.22 (br, 1H; fucosyl-H¹), 5.68 (d, *J* = 3.9 Hz, 1H; fucosyl-H¹), 6.59 (br, 1H; carbamate-NH), 7.02 (d, *J* = 6.2 Hz, 2H; aromatic), 7.11–7.34 ppm (m, 63H; aromatic); ¹³C NMR (125 MHz, CDCl₃, 20 °C): δ = 16.35, 20.67, 67.88, 68.22, 68.33, 69.32, 70.88, 72.25, 72.37, 72.40, 72.48, 72.51, 72.56, 72.95, 73.21, 73.39, 73.50, 73.70, 74.06, 74.38, 74.47, 74.66, 74.75, 75.02, 75.28, 75.34, 75.45, 75.47, 75.60, 70.82, 78.64, 79.37, 79.42, 83.79, 95.56, 95.60, 97.63, 98.05, 100.10, 100.13, 101.49, 126.01, 126.94, 126.96, 127.12, 127.16, 127.20, 127.26, 127.36, 127.42, 127.56, 127.63, 127.69, 127.78, 127.84, 127.87, 127.94, 127.99, 128.08, 128.12, 128.14, 128.19, 128.26, 128.33, 128.36, 128.40, 128.42, 128.48, 128.56, 128.61, 137.62, 137.71, 138.00, 138.04, 138.14, 138.39, 138.57, 138.68, 138.77, 139.02, 139.22, 139.32, 154.13, 154.30, 170.66, 174.14 ppm; MS (ESI): *m/z* calcd for C₁₄₇H₁₆₄Cl₆N₂O₃₆Na [*M*+Na]⁺ 2766, found 2766.

Experimental details for compounds **1** and **4–13** are described in the Supporting Information.

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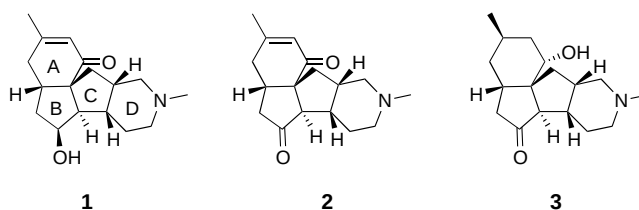
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Concise and Efficient Total Synthesis of *Lycopodium* Alkaloid Magellanine**

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An array of complex polycyclic alkaloids has been isolated from club mosses of the genus *Lycopodium* and these structures have posed a challenge for synthetic chemists.^[1] In the 1970s, the isolation and characterization of a group of closely related tetracyclic alkaloids, magellanine (**1**), magellaninone (**2**) (from *L. magellanicum*), and paniculatinone (**3**),



from *L. paniculatum* were reported by Castillo, MacLean, and co-workers.^[2] Owing to the intriguing structural features of these alkaloids, their synthesis remains a formidable challenge.

Magellanine (**1**), whose structure is characterized by a tetracyclic framework ABCD, contains two methyl groups, one carbonyl functionality, one double bond, and one hydroxy group on its periphery, and the piperidine ring D. Furthermore, this highly compact molecular architecture includes six contiguous stereogenic centers, one of which is a quaternary carbon atom. Not surprisingly, the structural novelty of the

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