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 CH_2Cl_2 (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 µL, 0.04 mmol) were added. The reaction was monitored by thin layer chromatography (TLC) (hexane/CH_2Cl_2/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 µL, 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. $NaHCO_3$) and solid sodium thiosulfate ($Na_2S_2O_3$). Molecular sieves were then filtered off and the filtrate was washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, and dried ($MgSO_4$). The concentrate was purified with flash column chromatography (toluene/CH_2Cl_2/EtOAc, 4:1:1) to give **14** (0.3 g, 44 %) as glassy white solid. ^{1}H NMR (600 MHz, $CDCl_3$, 20 °C): $\delta = 1.12$ (d, $J = 6.6$ Hz, 3H; fucosyl-CH_3), 1.24 (d, $J = 6.6$ Hz, 3H; fucosyl-CH_3), 1.34 (t, $J = 7.5$ Hz, 2H; aglycon-CH_2), 1.54–1.60 (m, 4H; aglycon-CH_2), 1.85 (s, 3H; $CH_3C{=}O$), 2.09 (s, 3H; $CH_3C{=}O$), 2.28 (dt, $J = 7.5$, 2.2 Hz, 2H; aglycon-CH_2), 2.34 (d, $J = 18$ Hz, 1H; lev-CH_2), 2.43 (d, $J = 19$ Hz, 1H; lev-CH_2), 2.63 (br, 1H; lev-CH_2), 2.79 (dd, $J = 18$, 8.0 Hz, 1H; lev-CH_2), 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-H^1), 5.68 (d, $J = 3.9$ Hz, 1H; fucosyl-H^1), 6.59 (br, 1H; carbamate-NH), 7.02 (d, $J = 6.2$ Hz, 2H; aromatic), 7.11–7.34 ppm (m, 63H; aromatic); ^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): $\delta = 16.35$, 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, 1011.49, 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 $C_{147}H_{164}Cl_6N_2O_{36}Na$ $[M+Na]^+$ 2766, found 2766.

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

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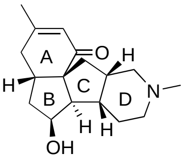
Concise and Efficient Total Synthesis of *Lycopodium* Alkaloid Magellanine[**]

Chi-Feng Yen and Chun-Chen Liao[*]

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. magellinicum*), and paniculatine (**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.



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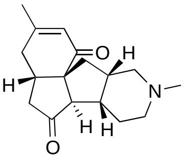

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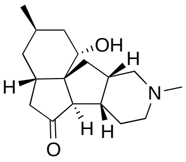

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Magellanine (**1**), whose structure is characterized by a tetracyclic framework ABCD, contains two methyl groups, one carbonyl functionality, one double bond, and one hydroxy group on its periphery, and the piperidine ring D. Furthermore, this highly 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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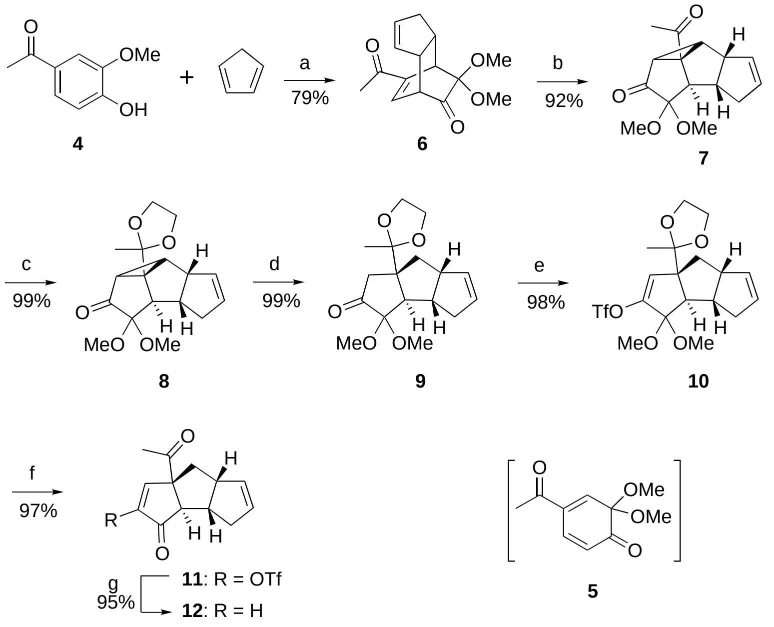
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

magellanine skeleton has evoked a great deal of attention from the synthetic community, and numerous studies have been directed at its total synthesis.[3] So far, the total synthesis of **1** was successfully accomplished by Overman and co-workers[4] (enantiomerically pure form) and Paquette et al.[5] (racemic form). Herein, we describe an efficient total synthesis of **1** in its racemic form from commercially available acetovanillone (**4**).

Recent synthetic efforts in our laboratories directed at the utilization of masked *o*-benzoquinones resulted in the successful acquisition of bicyclo[2.2.2]octenones, oxatricycles, triquinanes, and bicyclo[4.2.2]decenones, which are pivotal subunits in the construction of several natural products.[6] The present study highlights the efficacy of masked *o*-benzoquinone approach in the total synthesis of **1** via linear triquinane **9** (Scheme 1). We expected to complete the total synthesis of the title alkaloid by sequential elaboration of **9**, which contains the required BC rings with proper stereochemistry.

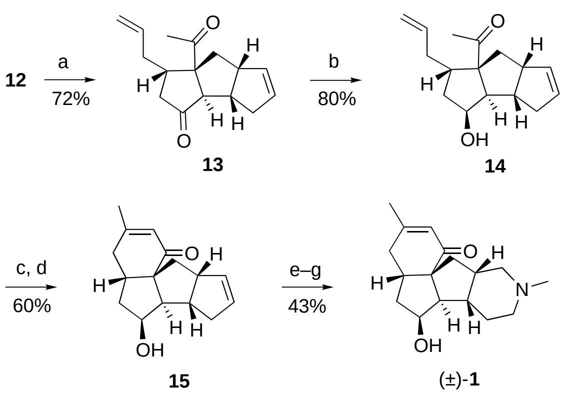
We planned to access the linear triquinane **9** by making use of a method that we recently developed[7] which includes a Diels–Alder reaction of masked *o*-benzoquinone followed by the oxa-di-π-methane (ODPM) rearrangement (Scheme 1). Thus, acetovanillone (**4**) was treated with cyclopentadiene in the presence of DAIB in methanol. The masked *o*-benzoquinone **5**, transiently generated from **4**, was trapped smoothly with cyclopentadiene at ambient temperature to provide a single cycloadduct **6**, in which the four contiguous stereogenic centers are fixed by the regio- and stereocontrolled Diels–Alder reaction. Irradiation of **6** in acetone with fluorescent lamps (RUL-3000 Å) through Pyrex filters in a Rayonet reactor afforded tetracyclic diketone **7** through the ODPM rearrangement[8] in excellent yield. The success of this transformation is the result of an appropriately positioned electron-withdrawing acetyl group in **6**.[7,9] The carbonyl group of the cyclopentane ring of **7** could serve both as an activating group for the opening of the cyclopropane ring and also to generate the required olefin. We foresee that the latent carbonyl functionality, present in the form of a dimethoxy acetal, is necessary for the Michael addition and for the further generation of an hydroxy group. At this stage, it was necessary to protect the carbonyl group of the aceto functionality in **7** for the selective opening of the cyclopropane ring. For this purpose, after considerable experimentation, the acetyl group was selectively protected under the conditions reported by Noyori and co-workers[10] to deliver monoacetal **8** in quantitative yield. Opening of the strained cyclopropane ring of **8** with tributyltin hydride/AIBN[11] led to the quantitative formation of linear triquinane **9**. Ketone **9** was then transformed into enol triflate **10** by using 2-pyridyltrifluoromethanesulfonimide.[12] Triflate **10** was exposed to hydrochloric acid to yield diketone **11**, which in turn was readily converted into triquinane **12** in excellent yield by reductive cleavage of the triflate group.[13]

With linear triquinane **12** secured, the stage was set for construction of the A ring. After several trials, it was possible to effect 1,4-addition of diallylcyanocuprate[14] to **12** to afford **13** in good yield and with stereoselective delivery of the allyl group exclusively from the less hindered α face (Scheme 2). The stereochemistry of **13** was confirmed by X-ray diffraction analysis.[15] Regioselective reduction of diketone **13** was effected by treatment with L-Selectride to generate β-alcohol **14**. This reduction is governed by the steric hindrance at the concave face of **13**, thus leading to the attack of hydride from the α face. The silyl enol ether generated from alkenyl methyl ketone **14** was subjected to intramolecular cyclization with oxa-π-allylpalladium(II) intermediates[16] to afford tetracyclic enone **15** in good yield.



Scheme 1. Synthesis of **12**. a) DAIB, MeOH, room temperature; b) *hν*, acetone, room temperature; c) $(CH_2OTMS)_2$, TMSOTf, CH_2Cl_2, −78 °C→RT; d) AIBN, $n\mathrm{Bu_3SnH}$, PhH, 80 °C; e) LHMDS, 2-PyNTf$_2$, THF,−78 °C; f) HCl (10 %), THF, 100 °C; g) $[\mathrm{PdCl_2(PPh_3)_2}]$, $\mathrm{HCO_2H}$, $n\mathrm{Bu_3N}$, DMF, 80 °C. DAIB = diacetoxyiodobenzene, TMS = trimethylsilyl, OTf = triflate = trifluoromethanesulfonate, AIBN = azobisisobutyronitrile, LHMDS = lithium hexamethyldisilazide, 2-PyNTf$_2$ = 2-pyridyltrifluoromethanesulfonimide, DMF = *N*,*N*-dimethylformamide.

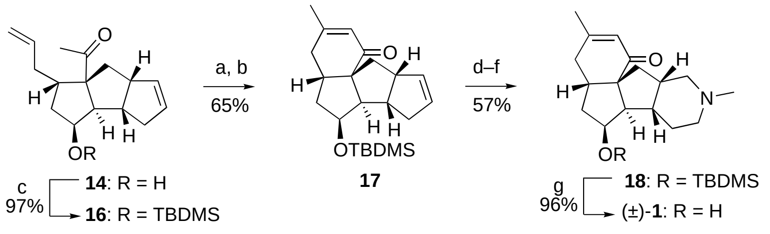
Having successfully introduced the requisite six stereogenic centers and the ABC ring system, all that remained to complete the synthesis of the targeted molecule was to convert the cyclopentene ring of **15** into piperidine ring D. Toward that objective, **15** was subjected to sequential regiospecific oxidative cleavage of cyclopentene ring with osmium tetraoxide/NMO and sodium periodate,[17] and double reductive amination[18] with methylamine hydrochloride to provide racemic magellanine (**1**). The NMR spectral data of (±)-**1** are in full consonance with those reported for the chiral molecule.[4,19] Furthermore, the assignment was supported by its HETCOR spectrum (see Supporting Information). Thus, synthesis of the target molecule was completed over 14 steps in 9 % overall yield (84 % average yield per step), which is much higher than that of the earlier reported routes.[4,5] Furthermore, unlike in the reported approaches, the starting materials used in the present study are commercially available and inexpensive.



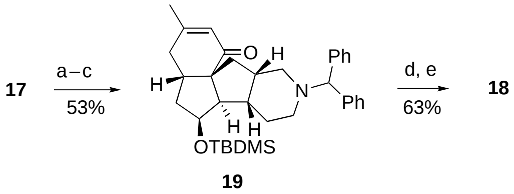
Scheme 2. Synthesis of magellanine (**1**): a) Allyltributyltin, *n*BuLi, CuCN, TMSCl, THF, −78 °C→RT; b) L-Selectride, THF, −78→−20 °C; c) LDA, TMSCl, THF, 0 °C→RT; d) $Pd(OAc)_2$, MeCN, room temperature; e) OsO_4, NMO, *t*BuOH/THF/H_2O (2.5:5:1), room temperature; f) $NaIO_4$, H_2O/CH_2Cl_2, room temperature; g) CH_3NH_3Cl, $NaBH_3CN$, IPA, 4-Å molecular sieves, room temperature. LDA = lithium diisopropylamide, NMO = *N*-methylmorpholine *N*-oxide, IPA = 2-propanol.

In an effort to render the synthetic route more efficient, we elected to conduct the cyclization of TBDMS ether **16**, derived from **14**, instead of the free alcohol **14**. Accordingly, **14** was protected as its TBDMS ether **16** and subjected to intramolecular cyclization to afford tetracycle **17**, which in turn was transformed into *N*-methylpiperidine **18** (Scheme 3). Finally, the facile deprotection[20] of TBDMS ether **18** afforded the target molecule. This new path allowed us to reach (±)-**1** in 16 steps in 12 % overall yield (87 % average yield per step). The stereochemistry of (±)-**1** was further confirmed by single-crystal X-ray structure analysis[21] of its *O*- and *N*-protected derivative **19**, which was formed from **17** (Scheme 4). The azatetracycle **19** was transformed into **18** by selective hydrogenolysis[22] followed by *N*-methylation.[23]

In summary, we have completed an efficient total synthesis of racemic magellanine (**1**). It illustrates the power of the masked *o*-benzoquinone Diels–Alder protocol and serves to show how highly condensed molecular architectures can be synthesized from simple 2-methoxyphenols. It is noteworthy that all 13 carbon atoms of the tricyclic skeleton **6**, including the aceto functionality, served in its elaborate functionalization to the target molecule. The other salient features of the current synthesis include the photochemical ODPM rearrangement, intramolecular cyclization of an alkenyl ketone, and the selective oxidative cleavage and double reductive amination. Although the present synthetic route leads to the racemic **1**, in principle, the enantiopure product can be obtained by means of kinetic resolution at different stages.



Scheme 3. Alternative route to **1** from **14**. a) LDA, TMSCl, THF, 0 °C→RT; b) $Pd(OAc)_2$, MeCN, room temperature; c) imidazole, TBDMSCl, DMF, room temperature; d) OsO_4, NMO, *t*BuOH/THF/H_2O (2.5:5:1), room temperature; e) $NaIO_4$, H_2O/CH_2Cl_2, room temperature; f) CH_3NH_3Cl, $NaBH_3CN$, IPA, 4-Å MS, room temperature; g) TBAF, THF, room temperature. TBDMS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, TBAF = tetrabutylammonium fluoride.



Scheme 4. Transformation of **17** into **18** via **19**. a) OsO_4, NMO, *t*BuOH/THF/H_2O (2.5:5:1), room temperature; b) $NaIO_4$, H_2O/CH_2Cl_2, room temperature; c) Ph_2CHNH_3Cl, $NaBH_3CN$, IPA, 4-Å molecular sieves, room temperature; d) 10 % Pd/C, 1,4-cyclohexadiene, EtOH, room temperature, e) HCHO, $NaBH_3CN$, MeCN, room temperature.

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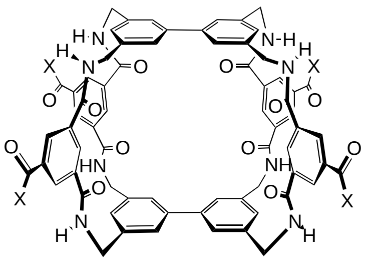
Highly Selective Disaccharide Recognition by a Tricyclic Octaamide Cage**

Grégory Lecollinet, Andrew P. Dominey, Trinidad Velasco, and Anthony P. Davis*

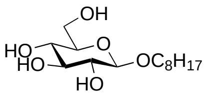
Carbohydrate recognition presents a continuing challenge to supramolecular chemistry,[1] fuelled by the growing awareness of saccharide structures as mediators of biological events.[2] However, while the biological interest is focussed largely on oligosaccharides, supramolecular chemists have concentrated mainly on monosaccharide substrates. A number of systems show preferential binding of di- versus monosaccharides,[1c–e,3] but only a few boron-based receptors show good selectivity between disaccharides.[1c,3a–3d] The latter employ covalent B–O bond formation, and are thus less relevant to biological carbohydrate recognition.

We recently described the tricyclic cage receptors **1**, which bind monosaccharide derivatives strongly and selectively even in the presence of a hydroxylic cosolvent.[4] Receptor **1** proved remarkably selective for the all-equatorial β-glucoside **2** as against the α-anomer **3**. We now report the synthesis and binding properties of **4**, an "extended analogue" of **1** designed to accommodate disaccharide substrates. Compound **4** has proved to be the first receptor capable of distinguishing clearly between disaccharides through noncovalent interactions.

Receptor **4** was synthesized by two independent routes. In the first, the tetraaminoterphenyl **5** was prepared as shown in Scheme 1 and coupled under high dilution with bis(penta-



1 X = OC_5H_{11} or $NHC(CH_2OBn)_3$



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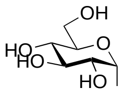

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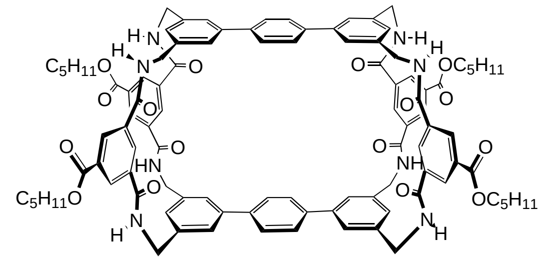

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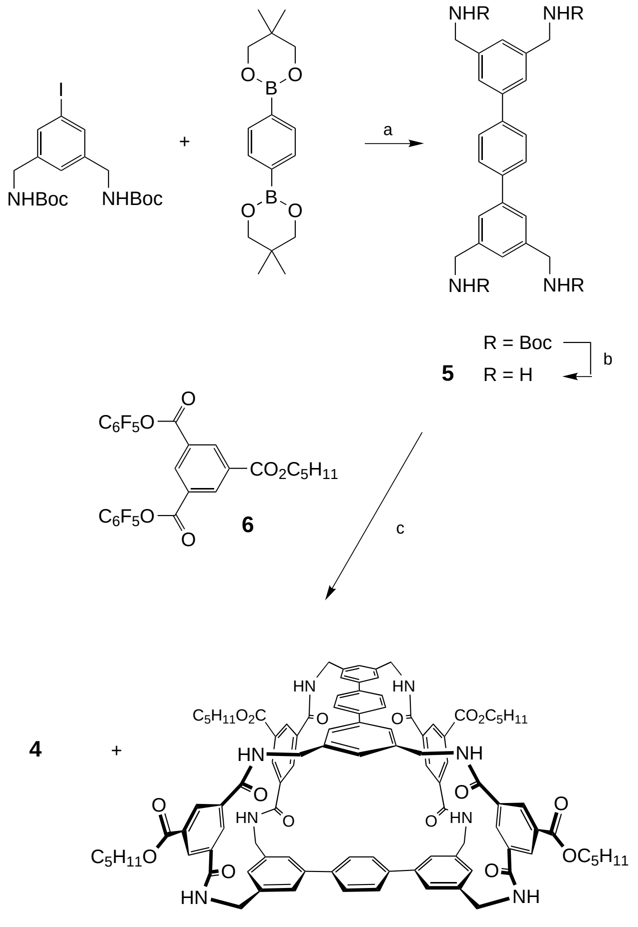

Scheme 1. Synthesis of **4** + **7**: a) $[PdCl_2(dppf)]$, Na_2CO_3 aq. (2 M), DMF, 80 °C; b) trifluoroacetic acid (TFA), CH_2Cl_2; c) **6**, $i$$Pr_2NEt$, THF/DMF, high dilution. dppf = diphenylphosphanylferrocene.

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