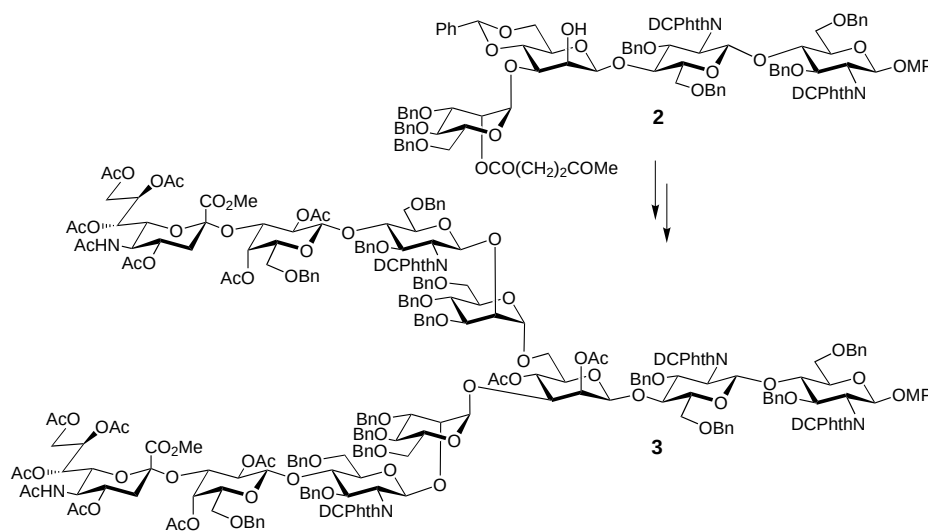


Synthesis of an α -(2,3)-Sialylated, Complex-Type Undecasaccharide**

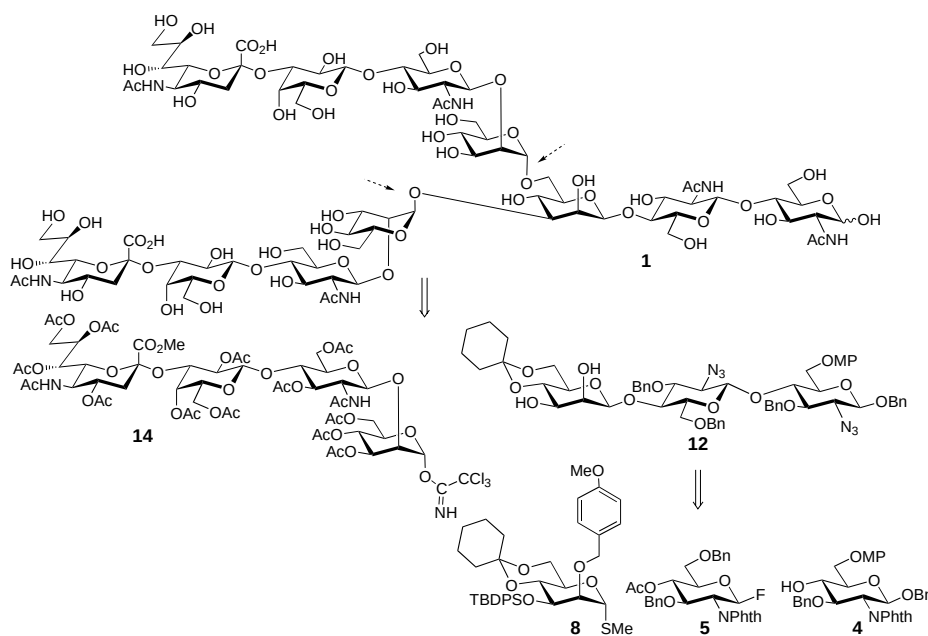
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N-Glycosylation is a widespread posttranslational modification of eukaryotic proteins. N-Glycans are functional constituents of glycoproteins and serve to control the intra- and intercellular distribution and three-dimensional structure of glycoproteins and also protect them against degradation. Furthermore, N-glycans are involved in important biological processes including cell differentiation, cell adhesion, and malignant transformation.^[1] Here we report the synthesis of undecasaccharide **1** (see Scheme 2), one of the prototypical structures of complex-type N-glycans of mammalian origin.^[2] This represents the first purely chemical synthesis of **1** achieved with strict stereochemical control.^[3]

With the aim of constructing this complex molecule in a stereocontrolled fashion, our initial investigation centered around the use of tetrasaccharide **2**^[4a] (Scheme 1), obtainable by *p*-methoxybenzyl-assisted intramolecular aglycon delivery (IAD), as the key intermediate, which was eventually transformed into the fully protected undecasaccharide **3**. However, deprotection of **3** turned out to be highly challenging, mainly due to the difficulty of manipulating sialic acid methyl ester in the presence of a 4,5-dichlorophthaloyl (DCPhth) group, and vice versa.



Scheme 1. The tetrasaccharide **2** served as a template for the formation of undecasaccharide **3**. The deprotection of **3** failed. Bn = benzyl, DCPhth = 4,5-dichlorophthaloyl, MP = *p*-methoxyphenyl.



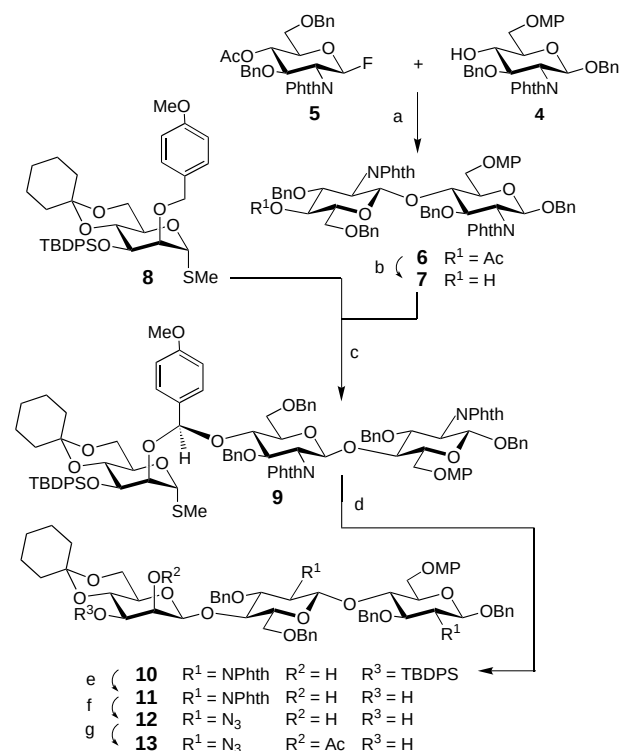
Scheme 2. The undecasaccharide **1** was constructed from the β -mannosidic trisaccharide **12** and trichloroacetimidate **14**^[11] as key building blocks. Compound **12** was prepared from the monosaccharides **4**,^[5b,c] **5**^[5d] and **8**.^[5a] Phth = phthaloyl, TBDPS = *tert*-butyldiphenylsilyl.

In our revised synthetic plan (Scheme 2), the core trisaccharide **12** was designed as the key intermediate on the basis of the following considerations: First, acetamido groups were masked as azides in the hope that problems associated with the potential nucleophilicity of acetamido groups and/or the base lability of phthalimide (or DCPhth) can be largely eliminated at the stage of critical glycoside bond forming reactions and/or manipulation of the protecting groups. Additionally, to maximize the efficiency of β -mannosylation, cyclohexylidene-protected **8**^[5a] was adopted as the mannosyl donor; it has proved to be the most suitable glycosyl donor for such purposes.

In practice, preparation of trisaccharide **12** was executed with monosaccharide components **4**,^[5b,c] **5**,^[5d] and **8**^[5a] (Scheme 3) and commenced with the high-yield preparation

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Scheme 3. a) $[\text{Cp}_2\text{HfCl}_2]$, AgOTf, molecular sieves (4 Å), CH_2Cl_2 , -30°C ; b) NaOMe, MeOH (75 %, 2 steps); c) DDO (1.5 equiv), molecular sieves (4 Å), CH_2Cl_2 , 2 h; d) MeOTf (3.4 equiv), DBMP (3.8 equiv), molecular sieves (4 Å), $\text{ClCH}_2\text{CH}_2\text{Cl}$, 45°C , 36 h (78 %); e) TBAF, HOAc, THF (78 %); f) 1. ethylenediamine, *n*-BuOH, 100°C , 24 h, 2. Tf- N_3 , DMAP, CH_3CN , CH_2Cl_2 , 5 h (84 %); g) 1. $\text{CH}_3\text{C}(\text{OEt})_3$, *p*-Tos-OH/ OH_2 , C_6H_6 , 1 h, 2. 80 % HOAc, 5 min (92 %). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DBMP = 2,6-di-*tert*-butyl-4-methylpyridine, DMAP = 4-dimethylaminopyridine, OTf = trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride, *p*-Tos-OH/ OH_2 = *p*-toluenesulfonic acid monohydrate, Tf- N_3 = trifluoromethanesulfonyl azide.

of chitobiose derivative **6** under Suzuki conditions.^[6] Subsequent deacetylation gave **7**, which in turn was subjected to β -mannosylation. Coupling with methylthio mannoside **8** according to our two-step protocol for IAD^[4, 5a] effected clean formation of β -mannoside **10** via mixed acetal **9** in 78 % yield. The $^1\text{J}(\text{C}, \text{H})$ coupling constant of C-1³ (161.7 Hz, Table 1) confirmed the configuration of the newly generated β -mannosidic linkage.^[7] Reaction of **10** with tetrabutylammonium fluoride (TBAF) led to the diol **11**. Subsequent removal of the phthaloyl group^[8] followed by a diazo transfer reaction^[9] afforded bisazido compound **12** in 84 % yield. Regioselective acetylation at position C-2³ was performed under Lemieux conditions^[10] to furnish **13** in high yield.

Trichloroacetimidate **14** (Scheme 2), which corresponds to symmetric branches linked to mannose,^[3] was prepared as described previously.^[11] The glycosylation of 2³-O-acetylated **13** with **14** (1.9 equiv) provided **16** in 69 % yield (Scheme 4). Alternatively, a similar reaction with diol **12** gave 3-O-glycosylated **15** as the sole isolable coupling product in 61 % yield, which was acetylated to **16**. Removal of the cyclohexylidene group to give diol **17** was followed by further glycosylation to undecasaccharide, again with trichloroacetimidate **14** as glycosyl donor. This reaction gave the undeca-

Table 1. Selected physical data of **1**, **10**, **15**, **16**, **18**, and **19**

1: $[\alpha]_D^{20} = -2.1$ ($c = 0.33$ in H_2O); ^1H NMR (500 MHz, D_2O , 25°C , *t*BuOH): $\delta = 5.19$ (d, $^3\text{J}(1,2) = 2.7$ Hz, 0.67 H; H-1^{1a}), 5.11 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1 H; H-1^{1b}), 4.92 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1 H; H-1⁴), 4.75 (d, $^3\text{J}(1,2) < 1.0$ Hz, 1 H; H-1³), 4.69 (d, $^3\text{J}(1,2) = 7.8$ Hz, 0.33 H; H-1^{1b}), 4.61 (d, $^3\text{J}(1,2) = 7.8$ Hz, 0.67 H; H-1^{2b}, α form), 4.60 (d, $^3\text{J}(1,2) = 7.6$ Hz, 0.33 H; H-1^{2b}, β form), 4.57 (d, $^3\text{J}(1,2) = 8.0$ Hz, 2 H; H-1^{5/5}), 4.55 (d, $^3\text{J}(1,2) = 7.8$ Hz, 1 H; H-1^{6b}), 4.54 (d, $^3\text{J}(1,2) = 7.8$ Hz, 1 H; H-1^{6b}), 4.24 (dd, $^3\text{J}(2,3) = 2.4$ Hz, 1 H; H-2³), 4.19 (dd, $^3\text{J}(2,3) = 3.0$ Hz, 1 H; H-2⁴), 4.13–4.10 (m, 3 H; H-2⁴, H-3^{6/6}), 2.75 (dd, $^3\text{J}(3,4) = 4.3$ Hz, $^2\text{J}_{\text{gem}} = 12.3$ Hz, 2 H; H-3eq^{NN}), 2.08–2.03 (6s, 18 H; NAc), 1.80 (t, $^3\text{J}(3,4) \approx ^2\text{J}_{\text{gem}} = 12.0$ Hz, 2 H; H-3ax^{NN}); ^{13}C NMR (125 MHz, D_2O , 25°C , *t*BuOH): $\delta = 175.71$ – 174.53 (C=O), 103.34 (C-1⁶), 103.30 (C-1⁶), 102.06 (C-1²), 101.08 (C-1³), 100.52 (C-2^{NN}), 100.23 (C-1⁴, C-1⁵), 100.17 (C-1⁵), 97.77 (C-1⁴), 95.50 (C-1^{1b}), 91.12 (C-1^{1a}), 40.33 (C-3^{NN}), 23.03–22.57 (NAc); ESI-MS (neg. mode, MeOH/ $\text{H}_2\text{O} = 1/1$): m/z : 1110.7 $[(M^- - 2\text{H})/2]$; calcd for $\text{C}_{84}\text{H}_{136}\text{N}_6\text{O}_{62}/2$ $[(M^- - 2\text{H})/2]$: 1110.9

10: $[\alpha]_D^{20} = 19.9$ ($c = 2.67$ in CHCl_3); ^1H NMR (400 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.17$ (d, $^3\text{J}(1,2) = 8.2$ Hz, 1 H; H-1^{1b}), 4.96 (d, $^3\text{J}(1,2) = 8.1$ Hz, 1 H; H-1^{2b}), 4.33 (d, $^3\text{J}(1,2) < 1.5$ Hz, 1 H; H-1³), 1.08 (s, 9 H; CH_3); ^{13}C NMR (100 MHz, CDCl_3 , 25°C , TMS): $\delta = 100.04$ (C-1³, $^1\text{J}(\text{C}, \text{H}) = 161.7$ Hz), 99.70 (cyclohexylidene), 97.07 (C-1¹), 96.87 (C-1²), 26.96 (C(CH_3)₃), 19.39 (C(CH_3)₃)

15: $[\alpha]_D^{20} = -14.9$ ($c = 0.5$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 4.99$ (d, $^3\text{J}(1,2) = 2.1$ Hz, 1 H; H-1¹), 4.68 (d, $^3\text{J}(1,2) = 8.1$ Hz, 1 H; H-1^{6b}), 4.50 (d, $^3\text{J}(1,2) < 1.5$ Hz, 1 H; H-1³), 4.43 (m, 1 H; H-1⁵), 4.35 (m, 1 H; H-1¹), 4.28 (m, 1 H; H-1²), 3.91 (m, 1 H; H-2³); ^{13}C NMR (125 MHz, CDCl_3 , 25°C , TMS): $\delta = 101.08$ (C-1¹), 101.01 (C-1⁶), 100.45 (C-1²), 100.20 (cyclohexylidene), 99.97 (C-1⁵), 99.32 (C-1³, $^1\text{J}(\text{C}, \text{H}) = 162.2$ Hz), 98.78 (C-1⁴, $^1\text{J}(\text{C}, \text{H}) = 172.8$ Hz), 96.80 (C-2^N), 70.76 (C-2³); FAB-MS (pos. mode, NBA^[a]): m/z : 2461.0 $[M^+ + \text{H} + \text{Na}]$; calcd for $\text{C}_{115}\text{H}_{145}\text{N}_8\text{NaO}_{50}$ $[M^+ + \text{H} + \text{Na}]$: 2460.9

16: ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.10$ (m, 1 H; H-2³)

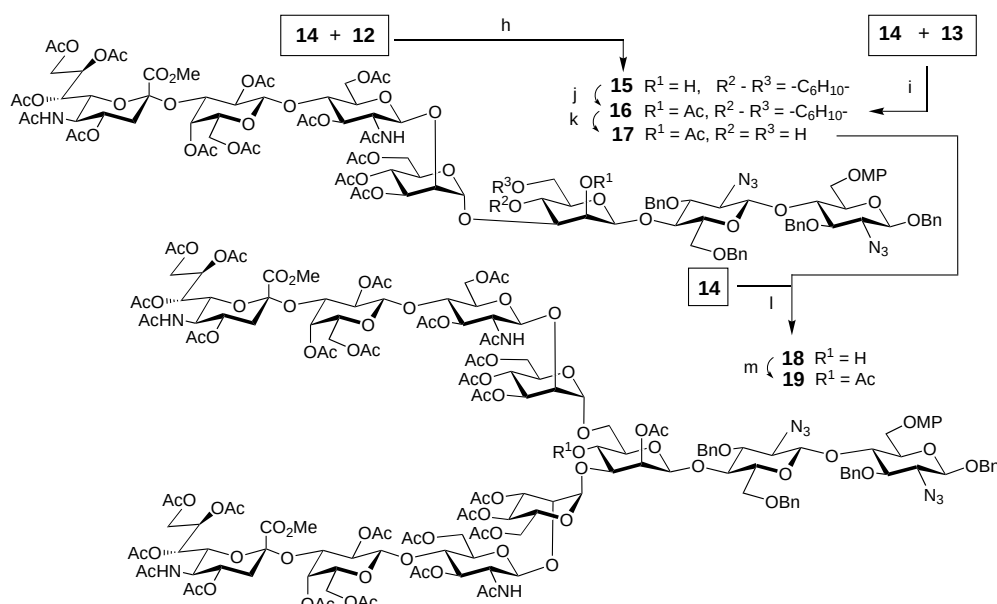
18: $[\alpha]_D^{20} = -9.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.10$, 4.64, 4.63, 4.59, 4.56, 4.43, 4.34, 4.30, 4.24 (H-1¹–H-1⁶ and H-1⁴–H-1⁶, not assigned), 3.74 (m, 1 H; H-4³); ^{13}C NMR (125 MHz, CDCl_3 , 25°C , TMS): $\delta = 101.17$, 100.88, 100.69, 100.47, 100.32, 99.95, 99.65 ($^1\text{J}(\text{C}, \text{H}) = 177.3$ Hz), 97.96, 97.79 ($^1\text{J}(\text{C}, \text{H}) = 170.8$ Hz), (C-1¹–C-1⁶ and C-1⁴–C-1⁶, not assigned), 96.74 (C-2^{NN}), 68.61 (C-4³); FAB-MS (pos. mode, NBA^[a]): m/z : 3759.8 $[M^+ + \text{H} + \text{Na}]$, calcd for $\text{C}_{167}\text{H}_{215}\text{N}_{10}\text{NaO}_{86}$ $[M^+ + \text{H} + \text{Na}]$: 3759.3

19: ^1H NMR (500 MHz, CDCl_3 , 25°C , TMS): $\delta = 5.03$ (dd, $^3\text{J}(3,4) \approx ^3\text{J}(4,5) = 8.8$ Hz, 1 H; H-4³)

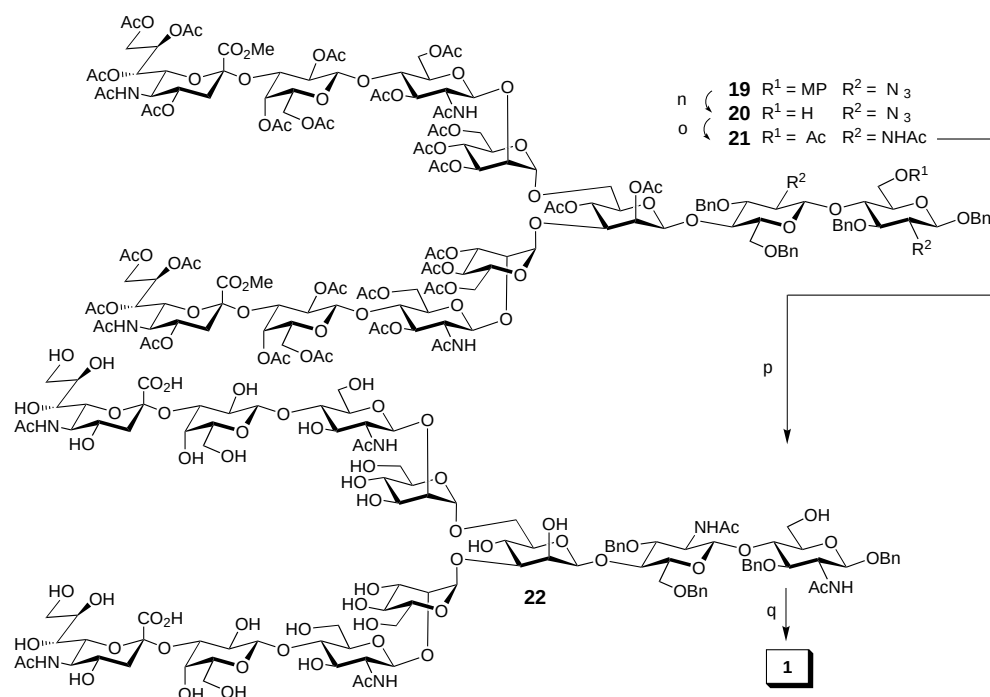
[a] NBA = *m*-nitrobenzyl alcohol. [b] $\delta(^1\text{H})$ was determined from a $^1\text{H}/^{13}\text{C}$ HMQC-COSY spectrum.

saccharide **18** in 50 % yield, which was counterbalanced by recovered **17**. Acetylation of **18** gave **19**, detailed ^1H NMR analysis of which fully supported its regio- and stereochemical integrity (Table 1).

Having obtained the full backbone structure of the target undecasaccharide, we executed complete deprotection of **19** (Scheme 5). First, the *p*-methoxyphenyl group at the reducing end GlcNAc residue was removed with ammonium cerium(IV) nitrate^[12] to afford **20**. Azido groups were converted into acetamides by a two-step procedure to give **21** in 82 % yield.^[13] Cleavage of the methyl ester and *O*-acetyl groups was performed under alkaline conditions to give **22**, which was finally subjected to hydrogenation over 10 % Pd/C. After purification by size exclusion chromatography (Biogel P-2, H_2O), the target molecule was isolated in 98 % yield. The ^1H NMR spectrum (500 MHz, Table 1) revealed that all chemical shifts of synthetic **1** are essentially identical with those reported for the reference compound **1** isolated from human chorionic gonadotropin.^[2a]



Scheme 4. h) TMS-OTf (0.2 equiv), molecular sieves (4 Å), CH₂Cl₂, -20 °C (61 %); i) BF₃/OEt₂ (1.5 equiv), CH₂Cl₂, molecular sieves (4 Å), -15 °C (69 %); j) Ac₂O, pyridine, DMAP (quantitative); k) *p*-Tos-OH/OH₂ (2.7 equiv), CH₃CN (92 %); l) BF₃/OEt₂ (2 equiv), molecular sieves (4 Å, AW 300), CH₂Cl₂, -20 °C (50 %); m) Ac₂O, pyridine, DMAP (92 %). TMS-OTf = trimethylsilyl trifluoromethanesulfonate.



Scheme 5. Deprotection of undecasaccharide **19** gives the target compound **1**. n) (NH₄)₂Ce(NO₃)₆, CH₃CN/toluene/H₂O (8/7/7), 0 °C, 15 h (80 %); o) 1. 1,3-propanedithiol, DIEA, pyridine/H₂O (7/3), 2. Ac₂O/pyridine (82 %); p) 1. NaOMe/MeOH, 12 h, 2. H₂O, 50 °C, 1 h; q) Pd/C (10 % Pd), H₂, MeOH/H₂O/HOAc (4/2/2), 5 h (98 %). DIEA = *N,N*-diisopropylethylamine.

In summary, we have achieved the convergent and stereocontrolled synthesis of the diantennary complex-type N-glycan **1**, which consists of eleven sugar residues and includes synthetically challenging sequences such as α -linked sialic acids and β -linked mannose. Our basic strategy may well be flexible enough to provide access to other decorated structures. Since undecasaccharide intermediates **18** and **20** have hydroxy groups that can be specifically liberated, synthetic

routes to bisecting GlcNAc- and 6-*O*-Fuc- containing structures can be readily conceived.

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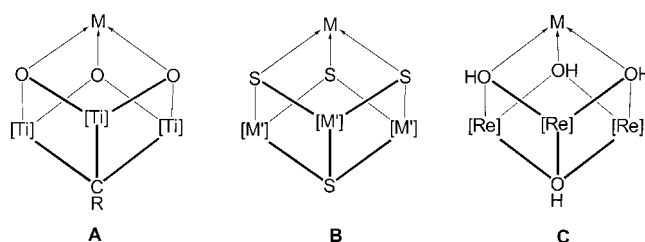
Construction of Heterometallic Cubanes

**$[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CR})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]$
 ($\text{R} = \text{H, Me}$; $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$) and
 $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{M}(\text{CO})_3\}]$
 ($\text{M} = \text{Cr, Mo, W}$); Crystal Structure of
 $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CMe})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]^{**}$**

Angel Abarca, Mikhail Galakhov, Pilar Gómez-Sal,
 Avelino Martín, Miguel Mena,* Josep-M. Poblet,
 Cristina Santamaría, and Jose Pedro Sarasa

*Dedicated to Alexander von Humboldt
 on the occasion of his commemorative year 1999*

Until now we have focused on the rich chemistry of alkylidyne groups on a trinuclear support without metal–metal bonds $[\{\text{TiCp}^*(\mu\text{-O})\}_3(\mu_3\text{-CR})]$ ($\text{R} = \text{H}$ (**1**), Me (**2**); $\text{Cp}^* = \eta^5\text{-C}_5\text{Me}_5$). We showed that metal carbonyl hydrides and unsaturated molecules such as carbon monoxide, isocyanides, and ketones are incorporated into the Ti_3O_3 core with direct participation of the alkylidyne units.^[1] In the course of our studies, we discovered that these complexes can also act as macrocyclic, tridentate six-electron donor ligands (Scheme 1, **A**) and thus provide an effective route to heterocubanes with $\text{MTi}_3(\mu_3\text{-CR})(\mu\text{-O})_3$ cores. To our knowledge, the only comparable behavior is the incorporation of metal ions by the

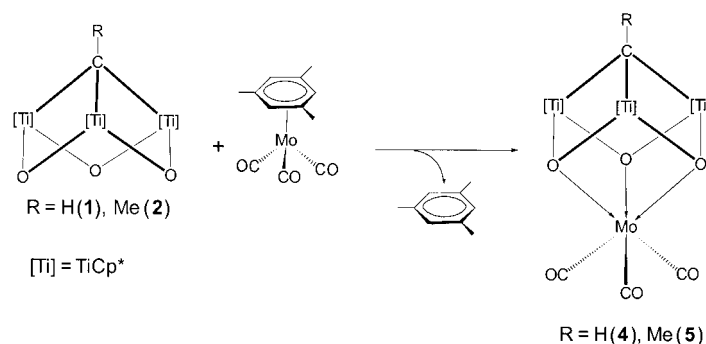


Scheme 1. Precubane systems as tripodal ligands.

$\text{M}'_3\text{S}_4$ ($\text{M}' = \text{Fe, Mo}$) precubane clusters (Scheme 1, **B**), which leads to heterometallic cubane-type $\text{MM}'_3\text{S}_4$ cores,^[2] and the hydroxymetalate complex $[\text{Re}_3(\text{CO})_9(\mu\text{-OH})_3(\mu_3\text{-OH})]$, which acts as a tripodal ligand (Scheme 1, **C**) to form “double-cubane” structures.^[3] Furthermore, the $(\mu_3\text{-CR})\text{Ti}_3(\mu_3\text{-O})_3\text{Mo}(\text{CO})_3$ cores described here could be invaluable as discrete and ideal models of oxide-supported metal carbonyl complexes for studying the catalyst–support interaction.^[4]

Here we report the formation of the heterometallic cubanes $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-CR})\}(\mu_3\text{-O})_3\{\text{Mo}(\text{CO})_3\}]$ ($\text{R} = \text{H}$ (**4**), Me (**5**)) and $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{Mo}(\text{CO})_3\}]$ (**6**) from $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ and the alkylidyne complexes **1** and **2** and the isoelectronic $[\{\text{TiCp}^*(\mu\text{-NH})\}_3(\mu_3\text{-N})]$ (**3**), respectively. Treatment of **3** with the hexacarbonyl complexes $[\text{M}(\text{CO})_6]$ ($\text{M} = \text{Cr, Mo, W}$) also leads to **6** and the analogous heterocubane derivatives $[\{\text{Ti}_3\text{Cp}^*(\mu_3\text{-N})\}(\mu_3\text{-NH})_3\{\text{M}(\text{CO})_3\}]$ ($\text{M} = \text{W}$ (**7**), Cr (**8**)).

Reaction of the trimetallic starting materials **1** and **2** with one equivalent of $[\text{Mo}(\text{CO})_3(1,3,5\text{-Me}_3\text{C}_6\text{H}_3)]$ ^[5] in hexane at 80 °C for four days led to displacement of the mesitylene ligand from molybdenum to afford in good yield the dark green crystalline heterocubanes **4** and **5**, respectively (Scheme 2). The solid compounds are stable under argon at room temperature but decompose slowly (months) in $[\text{D}_6]\text{benzene}$ with formation of **1** or **2**.^[6]



Scheme 2. Synthesis of the heterometallic cubane complexes **4** and **5**.

The ^{13}C NMR spectra of both complexes show one signal at $\delta \approx 227$ for the three equivalent terminal carbonyl groups and exhibit a downfield shift of the alkylidyne carbon signals ($\delta(\mu_3\text{-CR}) = 410.3$ (**4**), 434.8 (**5**) relative to **1** ($\delta(\mu_3\text{-CH}) = 383.2$) and **2** ($\delta(\mu_3\text{-CMe}) = 401.7$). In the IR spectra of these compounds, the three terminal CO groups give rise to two strong bands between 1915 and 1815 cm^{-1} , as expected for complexes containing a *fac*- $\text{Mo}(\text{CO})_3$ group.^[7]

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