Stereoselective Formation of Substituted Tetrahydropyrans by Reaction of Aldehydes with (η^3-Allyl)molybdenum Complexes

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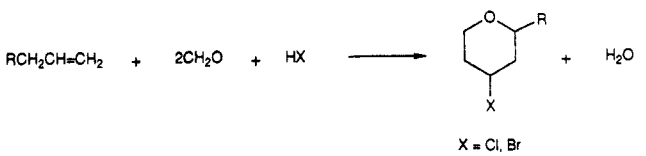
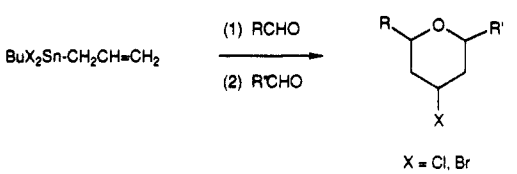
Summary: Substituted tetrahydropyrans are formed in high yield by condensation of 2 mol of aldehyde with molybdenum π-allyls. A [CpMo(NO)(η^3-allyl)(solvent)]$^+$-BF_4^- complex is a versatile reagent that provides a convenient route to certain tetrahydropyrans. This moderately stable η^3-allyl reagent is conveniently generated by silver-induced halide removal from CpMo(NO)(X)(η^3-allyl) complexes. The formation of single isomers of 4-fluoro 2,6-disubstituted tetrahydropyrans is a mild reaction, requiring 6–12 h for completion at room temperature. Spectroscopic evidence suggests intermediate formation of a [CpMo(NO)(allyl)(η^1-RCHO)]$^+BF_4^-$ complex.

The formation of 4-halo-substituted tetrahydropyrans (THP) is a common side reaction of conventional Prins reactions in aqueous media.[1] Modification of the Prins reaction with use of substantially anhydrous media led to the development of 3-alkyl-4-halotetrahydropyran synthesis from the condensation of α-olefins with paraformaldehyde and hydrogen halides:[2]



More recently 4-halo-substituted THP's have been observed as byproducts in the synthesis of homoallyl alcohols via allylsilanes[3,4] and allylhalostannane[5] reagents. The formation of substituted tetrahydropyrans via allylstannanation reagents has been extensively studied by Tagliavini,[5] who has developed a general method for 4-halo-substituted THP synthesis using aliphatic aldehydes. He has also shown that incremental addition of different aldehydes generates unsymmetrical THP's:

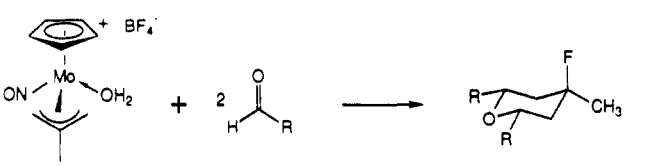


Taddei et al.[3] noted, during the preparation of homoallyl alcohols from the reaction of aldehydes with allyltrimethylsilane, that when $AlCl_3$ or $AlBr_3$ is used as the Lewis acid, the reaction generates high yields of 4-halo-substituted THP's with only trace amounts of homoallyl alcohols. Subsequent studies showed that consecutive addition of different aldehydes generated unsymmetrically 2,6-substituted tetrahydropyrans as well.[3]

Our investigation of substituted tetrahydropyran formation via condensation of 2 mol of aldehyde with molybdenum π-allyls suggests that the [CpMo(NO)(η^3-allyl)(S)]$^+$ solvento complex has potential as a versatile reagent in THP synthesis.

This moderately stable η^3-allyl reagent is conveniently generated in situ by silver-induced halide removal from CpMo(NO)(X)(η^3-allyl) complexes. If the solvent is not rigorously dried, water coordinates in the position from which halide was removed and the aqua complex, in reality, is usually the actual reagent. The formation of 4-fluoro 2,6-disubstituted tetrahydropyrans is a mild reaction requiring 6–12 h for completion at room temperature, with isolated yields ranging between 70 and 80%.

The reactions of [CpMo(NO)(η^3-2-methallyl)(S)]$^+$ are particularly informative. When the aromatic aldehydes *p*-anisaldehyde and benzaldehyde are used, the formation of the 4-fluoro-substituted THP's is highly stereoselective, yielding a single 4-fluoro 4-methyl 2,6-diaryl THP isomer. An X-ray crystal structure of 4-fluoro-4-methyl-2,6-bis(4-methoxyphenyl)tetrahydropyran (**1**) shows an all-cis configuration with the methyl and two 4-methoxyphenyl groups in the equatorial positions. This conformation is retained in solution, as evident from the ^{1}H NMR spectrum by analysis of the H–H and H–F couplings of the THP ring protons and the axial fluorine.[6] $J_{HF} \approx 40$ Hz for the protons on C-3(5) clearly indicates an axial fluorine at C-4. The large J_{HH} value for the C-2(6) and C-3(5) protons also indicates that the hydrogen on C-2(6) is axial. Likewise, analysis of the ^{1}H NMR spectrum of 4-fluoro-4-methyl-2,6-diphenyltetrahydropyran (**2**) reveals an all-cis configuration with the methyl and two phenyl groups equatorial. When cinnamaldehyde is used, the reaction yields predominately (93%) one isomer of 4-fluoro-4-methyl-2,6-distyryltetrahydropyran (**3**), which is also the all-cis isomer.



We also found that the unsymmetrically substituted 4-fluoro-4-methyl-2-(4-methoxyphenyl)-6-phenyltetrahydropyran (**4**) was produced in good yield by addition of a 1:1 mixture of the two aromatic aldehydes. The formation of this THP is also highly stereoselective, with the only observed isomer of **4** being the all-cis isomer. *Fur-*

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thermore, 4 is formed as 75% of the THP product mixture with the remainder being 1 and 2 as impurities; hence, this indicates a preference for formation of the unsymmetrical THP above that expected from statistics. Only the reaction of benzaldehyde with [CpMo(NO)(η^3-methallyl)]$^+$ produced substantial amounts of non-fluorinated THP products. This condensation could generate up to 70% of the two 4-hydroxy-substituted THP stereoisomers **5A,B** in a 1:1 ratio. The absence of fluorine in **5** was evident in the ^{1}H NMR spectrum, which showed a marked reduction in the number of resonances owing to the absence of H–F coupling to H_{3ax}, H_{3eq}, and the methyl group on C-4. The magnitude of J_{HH} between the C-2 and C-3 hydrogens indicated that the phenyl groups were equatorial, analogous to the case for the 4-fluoro-substituted derivatives. Thus, the two stereoisomers differ in the configuration at C-4.

When η^3-allyl was used instead of the 2-methallyl ligand, the reaction with 2 mol of benzaldehyde produced only the isomer of 4-fluoro-2,6-diphenyltetrahydropyran (**6**) that has the fluorine equatorial along with the phenyl substituents. This reversal of stereochemistry at C-4 for the η^3-allyl reaction may result from thermodynamic preferences; however, it may arise from the conformation of the allyl ligand in the starting material [CpMo(NO)(η^3-allyl)]$^+$. For the 2-methyl-substituted allyl complex, the allyl ligand is predominately in the endo conformation owing to the steric interaction between the Cp ring and the methyl group. This is a reversal of the observation when the η^3-allyl ligand is used. It has been shown that the exo conformation is the predominant species in an equilibrium mixture of the CpMo(NO)(CO)(η^3-allyl) cation ($K_{exo/endo}$ = 3.8 in acetone).[7]

An attractive mechanism for the formation of the tetrahydropyrans involves coordination of the aldehyde to the organometallic Lewis acid [CpMo(NO)(η^3-methallyl)]BF_4 to form [CpMo(NO)(η^3-methallyl)(η^1-RCHO)]BF_4. When the progress of the reaction with *p*-anisaldehyde was monitored by ^{1}H NMR spectroscopy ($CDCl_3$), the spectrum showed a bound aldehyde peak at δ 9.49 throughout the reaction. This modest upfield shift suggests an η^1-aldehyde analogous to [CpFe(CO)$_2$(η^1-isobutyraldehyde)]$^+$, where δ(HCO) is 9.58 ppm.[8] In metal η^2-aldehyde complexes, the aldehyde protons experience a much larger upfield shift in the ^{1}H NMR spectra. For example, in the cationic [CpRe(NO)(PPh_3)(η^2-OCH_2)]$^+$, the aldehyde protons resonate at δ 4.93 and 4.38.[9]

An η^1-allyl ligand would be expected to be in equilibrium with the more stable η^3-allyl. The open site created by the formation of the η^1-allyl group would allow the coordination of a second aldehyde. Attack by the η^1-allyl ligand on an activated aldehyde would ensue, forming a C–C bond and yielding a coordinated homoallylic alcoholate bound through oxygen and an η^2-olefin.[10] This activated double bond could then be attacked by fluoride. The details of the incorporation of the second molecule of aldehyde into the resulting molybdenum alkyl are obscure.

The high stereoselectivity observed for the formation of C-2 and C-6 is presumably a consequence of the preferred equatorial position of the bulky R groups during the formation of the six-membered ring. The stereoselectivity at the 4-fluoro-substituted carbon may be a result of selective BF_4^- addition from one side of the η^2-olefin intermediate. This most probably would be trans attack but could also involve coordination of BF_4^- to the metal before formation of the C–F bond.

Unlike the tetrahydropyran syntheses via allylstannanes and allylsilanes, the ability to resolve the chiral center by introduction of the neomenthyl group on the cyclopentadienyl ligand[10] allows the potential to produce nonracemic samples of unsymmetrically substituted tetrahydropyrans. We are currently investigating the potential of this reaction in asymmetric syntheses.

Experimental Section

Preparation of 4-Fluoro-4-methyl-2,6-bis(4-methoxyphenyl)tetrahydropyran (1). A typical procedure for the preparation of the substituted THP's is described for the preparation of 1. A CH_2Cl_2 solution (35 mL) of 0.1800 g (0.483 mmol) of CpMo(NO)(I)(η^3-methallyl) was stirred for 2 h with 0.1050 g (0.539 mmol) of $AgBF_4$. The resulting suspension was centrifuged, and the orange solution was decanted onto molecular sieves (2 Å). A 2-fold excess of *p*-anisaldehyde (0.195 g, 1.84 mmol) was added, and the solution was stirred overnight.

Removal of the solvent left a red-brown oil, from which the desired product was extracted with a 1:1 mixture of CH_2Cl_2 and pentane. The extracts were filtered through an alumina plug. Removal of the solvents yielded a yellow oil that was a mixture of the product THP and *p*-anisaldehyde. The excess aldehyde was removed either by pulling a vacuum overnight or purifying by preparative TLC (silica, CH_2Cl_2, R_f(1) ~0.3). The desired product was isolated as a pale yellow solid (0.1229 g, 77%). Crystals suitable for an X-ray analysis of 1 were grown from a CH_2Cl_2/hexane solution (mp 77 °C). A crystal that measured 0.25 × 0.25 × 0.13 mm was used. Diffraction measurements were made on a Rigaku AFC5S fully automated diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Preliminary indications of the unit cell based on 25 randomly selected reflections revealed a monoclinc cell with the following lattice parameters: a = 17.060 (1) Å, b = 5.0918 (3) Å, c = 20.630 (1) Å, and β = 95.848 (5)°. The space group, on the basis of the observed systematic extinctions, was assigned as $P2_1/n$, Z = 4, with one molecule of composition $C_{20}H_{23}O_3F$ forming the asymmetric unit. The volume was 1782.6 (2) Å^3, and the calculated density was 1.23 g/cm^3. There were 3004 reflections collected with $2\theta \leq 120°$; of those reflections 1394 (46%) with $I \geq 3\sigma(I)$ were observed. Full-matrix refinement of the non-hydrogen atoms and isotropic refinement of the hydrogens that were located in the difference Fourier resulted in R = 0.049 and R_w = 0.061. Anal. Calcd for $C_{20}H_{23}FO_3$: C, 72.71; H, 7.02. Found: C, 72.80; H, 7.07. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$): δ 7.33 and 6.86 (d, both 4 H, 2 –C_6H_4– groups, J = 8.9 Hz), 4.85 (dd, 2 H, $H_{2(6)ax}$, J = 11.9, 1.5 Hz), 3.78 (s, 6 H, 2 OCH_{3b} groups), 2.10 (ddd, 2 H, $H_{3(5)eq}$, J_{HH} = 14.2, 1.5 Hz, J_{HF} = 9.5 Hz), 1.68 (ddd, 2 H, $H_{3(5)ax}$, J_{HH} = 14.2, 11.9 Hz, J_{HF} = 39.9 Hz), 1.42 (d, 3 H, CH_{3a}, J_{HF} = 21.8 Hz). $^{13}C\{^1H\}_{BB}$ NMR (125.8 MHz, 25 °C, $CDCl_3$): δ 158.95, 134.55, 127.10, 113.71 (s, –C_6H_4–), 93.15 (d, C_4, J_{CF} = 166.4 Hz), 74.86 (s, $C_{2(6)}$), 55.25 (s, OCH_{3b}), 44.04 (d, $C_{3(5)}$, J_{CF} = 20.5 Hz), 27.54 (d, CH_{3a}, J_{CF} = 24.1 Hz).

Preparation of 4-Fluoro-4-methyl-2,6-diphenyltetrahydropyran (2) and 4-Hydroxy-4-methyl-2,6-diphenyltetrahydropyran (5A,B). The 2,6-diphenyl-substituted tetrahydropyrans were prepared analogously to 1, with benzaldehyde substituted for *p*-anisaldehyde at the appropriate step. The crude product consisted of anywhere from exclusively **2** to a 1:1:1 mixture of **2** and the 4-hydroxy THP's **5A,B**. The 4-fluoro THP was separated from the 4-hydroxy THP's via preparative TLC (silica, CH_2Cl_2, R_f(**2**) ~0.8–0.9, R_f(**5**) ~0.1–0.3). The 4-fluoro-substituted THP **2** was isolated as a pale yellow solid. Crystallization from CH_2Cl_2/hexane mixtures at –15 °C yielded colorless crystals melting at 94–98 °C. Anal. Calcd for $C_{18}H_{19}FO$ (**2**): C, 79.97; H, 7.08. Found: C, 79.86; H, 7.08. ^{1}H NMR for **2** (490 MHz, 30 °C, $CDCl_3$): δ 7.46–7.25 (mult, 10 H, 2 –C_6H_5 groups), 4.95 (dd, 2 H, $H_{2(6)ax}$, J = 11.8, 1.5 Hz), 2.18 (ddd, 2 H, $H_{3(5)eq}$, J_{HH} = 13.9,

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Table I. Induced Upfield Shifts Observed for THP Hydrogens (in ppm)[a]

	H_{2ax}	H_{3eq}	H_{3ax}	CH_{3a}
		Isomer **5A**		
with no lsr	4.59	1.98	1.77	1.57
with lsr	3.60	−0.03	−0.60	−0.43
$\Delta\delta$	0.99	2.01	2.37	2.00
		Isomer **5B**		
with no lsr	4.97	1.88	1.68	1.32
with lsr	3.54	0.48	0.78	0.19
$\Delta\delta$	1.43	1.40	0.90	1.13

[a] lsr = lanthanide shift reagent.

1.5 Hz, J_{HF} = 9.7 Hz), 1.71 (ddd, 2 H, $H_{3(5)ax}$, J_{HH} = 13.9, 11.8 Hz, J_{HF} = 39.2 Hz), 1.45 (d, 3 H, CH_{3a}, J_{HF} = 21.5 Hz). $^{13}C\{^1H\}_{BB}$ NMR for **2** (125.8 MHz, 25 °C, $CDCl_3$): δ 142.39, 128.41, 127.47, 125.82 (s, $-C_6H_5$), 93.07 (d, C_4, J_{CF} = 166.2 Hz), 75.22 (s, $C_{2(6)}$), 44.21 (d, $C_{3(5)}$, J_{CF} = 22.8 Hz), 27.53 (d, CH_{3a}, J_{CF} = 24.1 Hz). Anal. Calcd for $C_{18}H_{20}O_2$ (**5**): C, 80.56; H, 7.51. Found: C, 80.52; H, 7.57. ^1H NMR for **5A** (490 MHz, 30 °C, $CDCl_3$): δ 7.43–7.23 (mult, 10 H, 2 $-C_6H_5$ groups), 4.59 (d, 2 H, $H_{2(6)ax}$, J = 11.9 Hz), 1.98 (d, 2 H, $H_{3(5)eq}$, J = 13.4 Hz), 1.77 (app t, 2 H, $H_{3(5)ax}$, J = 12.5 Hz), 1.57 (s, 3 H, CH_{3a}), 1.52 (br s, <1 H, −OH). $^{13}C\{^1H\}_{BB}$ NMR for **5A** (125.8 MHz, 25 °C, $CDCl_3$): δ 142.26, 128.37, 127.54, 125.91 (s, $-C_6H_5$), 77.45 (s, $C_{2(6)}$) 76.74 (s, C_4), 48.25 (s, $C_{3(5)}$), 25.82 (s, CH_{3a}). ^1H NMR for **5B** (490 MHz, 30 °C, $CDCl_3$): δ 7.43–7.22 (mult, 10 H, 2 $-C_6H_5$ groups), 4.97 (d, 2 H, $H_{2(6)ax}$, J = 12.1 Hz), 1.88 (d, 2 H, $H_{3(5)eq}$, J = 14.1 Hz), 1.68 (app t, 2 H, $H_{3(5)ax}$, J = 13.0 Hz), 1.32 (s, 3 H, CH_{3a}), 1.25 (br s, <1 H, −OH). $^{13}C\{^1H\}_{BB}$ NMR for **5B** (125.8 MHz, 25 °C, $CDCl_3$): δ 142.94, 128.34, 127.24, 125.88 (s, $-C_6H_5$), 77.42 (s, $C_{2(6)}$), 75.24 (s, C_4), 46.53 (s, $C_{3(5)}$), 31.61 (s, CH_{3a}). IR data (CH_2Cl_2): ν_{OH} at 3592 cm^{-1}.

Determination of Stereochemistry at C-4 for 4-Hydroxy-4-methyl-2,6-diphenyltetrahydropyran (5A,B). To a $CDCl_3$ solution of **5A,B** was added in portions the lanthanide shift reagent $Pr(C_{10}D_{10}F_7O_2)_3$. After each addition, the induced upfield shift was monitored by ^1H NMR spectroscopy (490 MHz, 30 °C). The lanthanide-induced chemical shifts for each isomer are listed in Table I.

Preparation of 4-Fluoro-2,6-diphenyltetrahydropyran (6). A solution of 0.6065 g (1.944 mmol) of $CpMo(NO)(Br)(\eta^3$-allyl) dissolved in 35 mL of CH_2Cl_2 was stirred for 2 h with 0.3847 g (1.976 mmol) of $AgBF_4$. The resulting suspension was centrifuged, and the orange solution was decanted onto molecular sieves (2 Å). A 1.3-fold excess (0.56 g, 5.3 mmol) of benzaldehyde was added to the solution, and the mixture was stirred overnight at room temperature. Purification of the resulting brown suspension yielded 0.3613 g (73%) of product as a pale yellow solid. Crystallization of the product from CH_2Cl_2/hexane solutions at −15 °C yielded crystals of **6** melting at 85–89 °C. Anal. Calcd for $C_{17}H_{17}FO$: C, 79.66; H, 6.69. Found: C, 79.41; H, 6.74. ^1H NMR (490 MHz, 30 °C, $CDCl_3$): δ 7.44–7.25 (mult, 10 H, 2 $-C_6H_5$ groups), 5.00 (dtt, 1 H, H_{4ax}, J_{HH} = 11.2, 5.0 Hz, J_{HF} = 49.8 Hz), 4.56 (d, 2 H, $H_{2(6)ax}$, J = 11.7 Hz), 2.44 (ddd, 2 H, $H_{3(5)eq}$, J_{HH} = 12.3, 5.0 Hz, J_{HF} = 2.8 Hz), 1.82 (app quintet, 2 H, $H_{3(5)ax}$, J = 11.5 Hz). $^{13}C\{^1H\}_{BB}$ NMR (125.8 MHz, 25 °C, $CDCl_3$): δ 141.33, 128.31, 127.63, 125.79 (s, $-C_6H_5$), 89.39 (d, C_4, J_{CF} = 177.9 Hz), 77.74 (s, $C_{2(6)}$), 40.22 (d, $C_{3(5)}$, J_{CF} = 17.6 Hz).

Preparation of 4-Fluoro-4-methyl-2-(4-methoxyphenyl)-6-phenyltetrahydropyran (4). The nonsymmetric tetrahydropyran was prepared analogously to the symmetrically substituted THP's, except that a 1:1 mixture of *p*-anisaldehyde and benzaldehyde was used at the appropriate step. Purification generated a pale yellow solid that was predominately **4** (75%), with minor amounts of the symmetric THP's **1** and **2** as impurities. The desired nonsymmetric THP was separated via preparative TLC (silica, CH_2Cl_2, R_f(**4**) ~0.5). The product crystallized from Et_2O as a colorless solid melting at 93–95 °C. Anal. Calcd for $C_{19}H_{22}FO_2$: C, 75.72; H, 7.36. Found: C, 75.82; H, 7.35. ^1H NMR (500 MHz, 25 °C, $CDCl_3$): δ 7.42–7.22 and 6.87 (mult, 9 H, $-C_6H_5$) and $-C_6H_4-$ groups), 4.91 (dd, 1 H, H_{6ax}, J = 11.8, 2.3 Hz), 4.87 (dd, 1 H, H_{2ax}, J = 11.8, 2.3 Hz), 3.78 (s, 3 H, OCH_{3b}), 2.14 (ddt, 1 H, H_{5eq}, J_{HH} = 14.3, 2.3 Hz, J_{HF} = 9.7 Hz), 2.11 (ddt, 1 H, H_{3eq}, J_{HH} = 14.2, 2.3 Hz, J_{HF} = 9.7 Hz), 1.69 (ddd, 1 H, H_{5ax}, J_{HH} = 14.3, 11.8 Hz, J_{HF} = 39.6 Hz), 1.68 (ddd, 1 H, H_{3ax}, J_{HH} = 14.2, 11.8 Hz, J_{HF} = 39.6 Hz), 1.42 (d, 3 H, CH_{3a}, J_{HF} = 21.1 Hz). $^{13}C\{^1H\}_{BB}$ NMR (125.8 MHz, 25 °C, $CDCl_3$): δ 159.06, 134.56, 128.34, 127.41, 127.14, 125.82, 113.81 (s, $-C_6H_4-$ and C_6H_5 groups), 93.14 (d, C_4, J_{CF} = 165.9 Hz), 75.24 and 74.86 (s, C_2 and C_6), 55.28 (s, OCH_{3b}), 44.20 and 44.05 (d, C_3 and C_5, J_{CF} = 18.0 Hz and 18.4 Hz), 27.53 (d, CH_{3a}, J_{CF} = 24.6 Hz).

Preparation of 4-Fluoro-4-methyl-2,6-distyryltetrahydropyran (3). The distyryltetrahydropyran was prepared by analogously substituting *trans*-cinnamaldehyde at the appropriate step, with the exception that the reaction time was reduced to 5 h. Purification yielded the desired THP **3** (54%) as a pale yellow oil that was unstable toward polymerization at room temperature. The ^1H NMR spectrum (500 MHz, 25 °C, $CDCl_3$) shows the presence of two isomers in a 13:1 ratio: major isomer (93%), δ 7.40–7.20 (mult, 10 H, 2 $-C_6H_5$ groups), 6.67 (d, 2 H, β-styryl, J = 16.1 Hz), 6.25 (dd, 2 H, α-styryl, J = 16.1, 6.3 Hz), 4.48 (dd, 2 H, $H_{2(6)ax}$, J = 11.7, 6.3 Hz), 2.01 (dd, 2 H, $H_{3(5)eq}$, J_{HH} = 14.0 Hz, J_{HF} = 9.8 Hz), 1.57 (ddd, 2 H, $H_{3(5)ax}$, J_{HH} = 14.0, 11.7 Hz, J_{HF} = 39.2 Hz), 1.44 (d, 3 H, CH_{3a}, J_{HF} = 21.6 Hz); minor isomer (7%), δ 4.09 (dd, H_{2ax}, J = 11.4, 6.0 Hz). $^{13}C\{^1H\}_{BB}$ NMR (125.8 MHz, 25 °C, $CDCl_3$): δ 136.83, 130.94, 129.51, 128.54, 127.66, 126.53 (s, styryl carbons), 92.62 (d, C_4, J_{CF} = 166.4 Hz), 73.47 (s, $C_{2(6)}$), 42.02 (d, $C_{3(5)}$, J_{CF} = 20.5 Hz), 27.60 (d, CH_{3a}, J_{CF} = 24.1 Hz).

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Supplementary Material Available: A drawing and table of positional and thermal parameters for **1** (2 pages). Ordering information is given on any current masthead page.