An Approach to Serrulatane Diterpenes via endo-Selective Conjugate Nucleophilic Addition to Arene-Cr(CO)₃ Complexes

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ABSTRACT



Starting from a nonracemic planar-chiral arene tricarbonyl chromium complex, the serrulatane diterpenoid (+)-20-methoxy-serrulat-14-en-7,8diol was synthesized in a highly stereoselective fashion. The key step of the synthesis is an endo-selective conjugate nucleophilic addition of lithio-methylphenyl sulfone to a 1-ethylidene-tetralin-Cr(CO)₃ derivative. By employing different substrates and nucleophiles it was shown that the surprising and rather general endo selectivity must result from a unique complex induced proximity effect under participation of the Cr(CO)₃ moiety.

Serrulatane diterpenes, such as 1, 2, and 3 (Figure 1), were isolated from the leaves of certain Eremphila bushes occurring in western Australia.¹ These compounds are structurally related but stereochemically different to some marine diterpenoids, i.e., the helioporins² and the seco-pseudopterosins,³ which show an epimeric structure at C-11 and an opposite absolute configuration. Despite their interesting structural and biological features, such serrulatanes have received only little recognition by synthetic chemists in the past and only a single total synthesis of a racemic compound (rac-3) has been

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reported in the literature.⁴ This may reflect the difficulty of setting up the three stereocenters with the correct relative and absolute configuration.

We here report a short, efficient, and completely stereoselective entry toward compounds related to 1 by exploiting arene-Cr(CO)₃ chemistry.⁵ Moreover, we show that the unusual endo selectivity of conjugate nucleophilic addition⁶





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to 1-ethylidene-tetralin- $Cr(CO)_3$ derivatives, used as a key step in this synthesis, is rather general and must result from an unprecedented attracting interaction of the nucleophile with the metal carbonyl unit.

On the basis of the experience we had collected during our previous work on the syntheses of 11-*epi*-helioporin B (4)⁷ and the nor-*seco*-pseudopterosin aglycon,⁸ we considered complex **5** as a suitable precursor for **1** and related compounds. We envisioned that **5** could be prepared by nucleophilic addition/protonation from the 1-ethylidenetetralin complex **6**, which in turn should be accessible via **7** starting from the planar-chiral building block **8** (Scheme 1).



While the configuration at C-1 would be controlled by $Cr(CO)_3$ -assisted benzylic *exo* alkylation,⁹ the question was whether the attack of a suitable nucleophile would again occur in an *endo* fashion, as it was observed for a related substrate in the above-mentioned synthesis of **4**.⁷ As shown in Figure 2, such an *endo* addition of a nucleophile to **6** would result in the formation of a $Cr(CO)_3$ -stabilized benzylic anion of type **9**, which on protonation (from the *exo* face) would give rise to a product of type **10** possessing exactly the configuration found in natural serrulatanes such as **1**, **2**, and **3**.

Applying the protocols developed before in the enantiomeric series,⁷ the readily accessible, optically active complex (+)-8 (= 96% ee)¹⁰ was converted into the 1-ethylidene derivative **11** by CeCl₃-mediated addition of vinylmagnesium chloride, vinylogous ionic hydrogenation, and silylation



Figure 2. Stereochemical course of the nucleophilic *endo* addition to 6 and subsequent protonation

(protection) of the most acidic aromatic position. Benzylic alkylation of **11** with *n*-BuLi and chloromethyl(methyl)ether (MOMCl) and subsequent (in situ) desilylation with TBAF/ H_2O afforded **12** as a sole regio- and diastereomer. The aromatic methyl substituent was finally introduced by another deprotonation/alkylation sequence to afford the envisioned key intermediate **6** in good overall yield (Scheme 2).



^{*a*} Key: (a) CH₂=CHMgCl, CeCl₃, THF; (b) Et₃SiH, Me₂AlCl/ EtAlCl₂, CH₂Cl₂; (c) *n*-BuLi, TMSCl, THF; 35–65% (3 steps); (d) *n*-BuLi, THF/HMPA (12:1), -70 to 0 °C, 1.5 h then MOMCl, -78 °C, 0.5 h; then H₂O, TBAF, 0 °C, 1.5 h; (e) *n*-BuLi, THF, -78 °C, 1 h then MeI; 65% (2 steps).

Treatment of **6** with 2-lithio-acetonitrile (prepared from MeCN and LDA in THF) in dioxane/HMPA at 5 °C afforded a mixture of the diastereomeric conjugate addition products **13a/13b** (d.r. = 12:1; HPLC) in 43% yield. Additionally, significant amounts (36%) of the nucleophilic *ipso*-substitution product **14** were obtained (Scheme 3).¹¹ When lithiomethylphenyl sulfone was used as a nucleophile under similar conditions, the diastereomerically pure *endo* addition product **15** was formed in good yield, and only traces of a substitution product corresponding to **14** could be detected by NMR.

The stereochemical assignments were unambiguously confirmed by X-ray crystallography of the (main) addition products **13a** and **15**.

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⁽¹¹⁾ Byproducts resulting from S_NAr reactions of OMe groups are occasionally observed in arene-Cr(CO)₃ chemistry; see for instance: (a) Reference 7. (b) Rose-Munch, F.; Chavingnon, R.; Tranchier, J.-P.; Gagliardini, V.; Rose, E. *Inorg. Chim. Acta* **2000**, *300–302*, 693. For recent reviews see: (c) Rose-Munch, F.; Gagliardini, V.; Renard, C.; Rose, E. Coord. Chem. Rev. **1998**, *178–180*, 249. (c) Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem.* **2002**, 1269.



^{*a*} Key: (a) LiCH₂CN, 1,4-dioxane/HMPA (5:1), 5 °C, 1 h, then NH₄Cl/H₂O, rt, 43% of **13a/13b** (d.r. = 12:1); 36% of **14**; (b) LiCH₂SO₂Ph, 1,4-dioxane/HMPA (5:1), 5 °C to room temperature, 4 h (d.r. \geq 97:3); (c) sunlight, air, MTBE, rt, 55% (over 2 steps).

Having found suitable conditions for performing the crucial conjugate addition to 6, the sulfone 16, obtained from the primary addition product 15 by decomplexation, was further converted as shown in Scheme 4.



^{*a*} Reagents and conditions: (a) *n*-BuLi, THF/HMPA (10:1), -78 °C, 1.5 h, then prenyl bromide, -78 °C, 15 min, 82% (d.r. = 3:1); (b) Na/Hg (5% Na), MeOH/THF (1:1), rt, 18 h, 84%; (c) LiSEt, DMF, 145 °C, 4h, 99%.

The completion of the side chain (as it is found in 1) was achieved by α -alkylation of the sulfone function with prenyl bromide to give 17 as a mixture of diastereomers. Desulfurization with sodium amalgam provided the trimethoxyserrulatane 18 in good yield. Treatment of 18 with LiSEt in refluxing DMF¹² cleanly led to cleavage of the aryl methyl ethers providing (+)-19 ([α]_D +17.2, *c* 0.51 in CHCl₃) in almost quantitative yield (Scheme 4).¹³ This way, the monomethyl ether of 1 was synthesized from the chiral building block 8 in only 10 steps with 15% overall yield.

Having thus demonstrated the power of the chosen strategy for the efficient and highly stereoselective synthesis of serrulatanes of type **1**, we were still puzzled about the nature of the observed *endo* selectivity in the nucleophilic addition to the double bond of **6**.¹⁴

On first glance, one may be tempted to explain the observed *endo* selectivity using simple steric arguments.⁷ Indeed, the X-ray crystal structure of substrate **6** (Figure 3)



Figure 3. Two conformers of 6 in the crystalline state.

indicates some hindrance of the *exo* attack by the pseudoaxial methoxymethyl substituent. However, it is not obvious at all why the *endo* attack should be favored for steric reasons, even in the one conformer (Figure 3, right) where the ethylidene unit is deviated out of the aromatic plane away from the shielding $Cr(CO)_3$ tripod.

To investigate the influence of the pseudoaxial substituent on the selectivity in the conjugate addition to 1-ethylidenetetralin- $Cr(CO)_3$ derivatives such as **6**, we decided to employ related compounds lacking a shielding benzylic substituent (Scheme 5).



Initial attempts to react complex ent- 7^7 with the nucleophiles used above resulted in the exclusive formation of nucleophilic substitution products related to 14. However, the methylated derivative 20a (prepared from ent-7 with *n*-BuLi/MeI) underwent the desired conjugate addition to afford mixtures of the *endo* and *exo* products 21a and 22a in acceptable yields (Scheme 5, Table 1). Only minor amounts (=15%) of nucleophilic substitution products were formed in these cases. The unsubstituted (parent) 1-ethylidene-tetralin complex 20b also reacted with nucleophiles in a conjugate fashion.

As suitable nucleophiles, a series of lithiated nitriles and lithio-methylphenyl sulfone were studied. While certain reactions proceeded smoothly in THF, mixtures of THF or 1,4-dioxane with HMPA were necessary in most cases to

⁽¹²⁾ LiSEt was prepared from n-BuLi and EtSH, see also ref 2b.

⁽¹³⁾ Initial attempts to cleave all three methoxy groups in 18 in one step (using reagents such as BBr₃, TMSI, or AlCl₃/DMS) were not successful.

⁽¹⁴⁾ It is a generally accepted rule in arene-Cr(CO)₃ chemistry that nucleophiles attack the ligand from the *exo* face. For rare exceptions, see ref 7 as well as: (a) Schmalz, H.-G.; Jope, H. *Tetrahedron* **1998**, *54*, 3457. (b) Sarkar, A.; Ganesh, S.; Sur, S.; Mandal, S. K.; Swamy, V. M.; Maity, B. C.; Kumar, T. S. J. Organomet. Chem. **2001**, *624*, 18.

Table 1. Results of the Nucleophilic Additions Employing Substrates **20a** and **20b** According to Scheme 5^a

entry	substrate	Li-Nuc	conditions ^a	yield (%) ^b	ratio ^c 21/22
1	20a	LiCH ₂ CN	А	39	92:8
2	20a	LiCH ₂ SO ₂ Ph	Α	57	>98:2
3	20a	LiCH(TMS)CN	В	68	$78:22^{d}$
4	20a	LiCMe ₂ CN	С	82	35:65
5	20b	LiCH ₂ CN	С	72	>98:2
6	20b	LiCH ₂ SO ₂ Ph	Α	47	82:18
7	20b	LiCH(TMS)CN	В	75	$> 98:2^{d}$
8	20b	LiCMe ₂ CN	Α	86	15:85
9	20b	LiCMe ₂ CN	С	62	10:90

^{*a*} A: Li-Nuc, 1,4-dioxane/HMPA (5:1), 5 °C to rt, 1.5 to 16 h (TLC control). B: Li-Nuc, THF/HMPA (5:1), -78 °C to rt, 2.5 to 4 h (TLC control). C: Li-Nuc, THF, -78 °C to room temperature, 1.5 to 4 h; ^{*b*} Isolated yield of the purified diastereomeric mixture. ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by ¹H NMR after desilylation (CsF, MeCN).

obtain significant conversions. The results of the various experiments are summarized in Table 1.

The stereochemical assignments are based on X-ray crystal structure analyses of compounds **21a** (Nuc = CH_2SO_2Ph), **22a** (Nuc = CMe_2CN), and **22b** (Nuc = CMe_2CN) in combination with NMR spectroscopic correlations.

As shown in Table 1 all the reactions employing LiCH₂-CN, LiCH₂SO₂Ph, or LiCH(TMS)CN¹⁵ as a nucleophile proceeded with a pronounced *endo* selectivity—in analogy to the results obtained with substrate **6**. Only with LiCMe₂-CN as a sterically more demanding nucleophile were the *exo* products preferentially formed.

These results allow the conclusion that the substituent in the benzylic position (as in 6) exerts no significant influence on the stereochemical course of the addition reactions. Moreover, it becomes apparent that the unusual *endo* selectivity cannot be attributed to steric effects, as the ("normal") *exo* pathway becomes predominant with increasing bulkiness of the nucleophile.

The preference for the *endo* attack must consequently result from an attracting interaction (kinetic effect). We



Figure 4. Preferred *endo* addition through precoordination of the nucleophile to a carbonyl ligand.

assume that the (smaller) nucleophiles are guided to the *endo* face of the double bond through coordination of the lithium atom to a carbonyl ligand (Figure 4). While such *complex induced proximity effects*¹⁶ are rather common in reactions of organolithium compounds with organic molecules bearing polar functional groups, it has (to the best of our knowledge) never been observed that carbonyl ligands of arene-Cr(CO)₃ complexes are able to participate in such processes.¹⁷

In summary, we have explored the stereochemical course of conjugate nucleophilic additions to 1-ethylidene-tetralin- $Cr(CO)_3$ complexes and have corroborated the surprising *endo* preference as a rather general phenomenon. While the synthetic value of such reactions was demonstrated in an efficient synthesis of a serrulatane diterpenoid, mechanistic considerations led to the identification of a unique *endo*directing role of the $Cr(CO)_3$ group, i.e., the active participation of a carbonyl ligand as a lithium-coordinating site.

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Supporting Information Available: Experimental procedures and characteristic data for all new compounds and details of the X-ray crystal structure analyses of compounds 6, 13a, 15, *ent-*7, 21a (Nuc = CH_2SO_2Ph), 22a (Nuc = CMe_2CN), and 22b (Nuc = CMe_2CN). This material is available free of charge via the Internet at http://pubs.acs.org.

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