ORGANIC LETTERS

2004
Vol. 6, No. 22
3937−3940

Cobalt(I)-Mediated [2 + 2 + 2] Cyclization of Allenediynes toward a Diastereoselective Approach to 11-Aryl Steroid Skeletons

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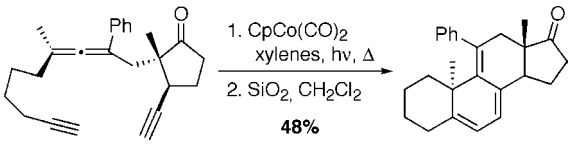
Received July 29, 2004

ABSTRACT



An 11-aryl steroid skeleton has been built in one step with a simultaneous introduction of the substituents at both C11 and C10 in 48% overall yield from a *trans*-allenediyne, whereas a formal Alder ene reaction leading to a bicyclic yne-trienic compound becomes the major process from the *cis*-allenediyne.

In the past 20 years, the synthesis, biological evaluation, and clinical applications of an entirely new class of antiprogestational steroids have emerged.[1] One of the primary structural features of such steroids is the presence of an 11β-aryl moiety.[2] Due to their industrially relevant pharmacological properties, a large number of synthetic efforts aimed at producing new compounds has been reported.[3] However, the synthesis of 11β-aryl steroids is still very much in need of the development of new methods.

In the course of our ongoing program based on metal-catalyzed or radical cyclization cascades directed toward the elaboration of basic skeletons of natural products,[4] we have explored the feasibility of building 11-aryl steroid frameworks by using an intramolecular cobalt(I)-mediated [2 + 2 + 2] cyclization of allenediynes.

The use of transition metal-mediated cyclizations[5,6] is certainly not new in the synthesis of the steroid nucleus. Indeed, the cobalt(I) synthesis of racemic estrone is the paramount illustration of the potency of this method.[7] In

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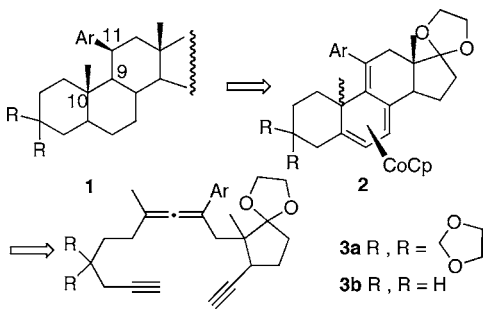
10.1021/ol0485060 CCC: $27.50
Published on Web 10/01/2004

addition, intramolecular cyclizations of enediynes that allow the simultaneous formation of either the BCD or ABCD ring systems have been proposed.[8] Although 11-trimethylsilyl-substituted steroid frameworks have been described,[9] only one example of a low-yielding access to the 11-α-hetero-substituted steroid skeleton has been reported. Our retrosynthetic plan is depicted in Scheme 1.

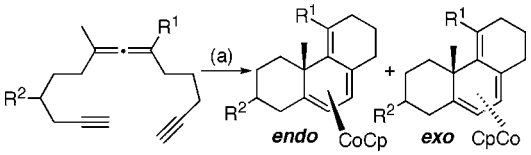
Scheme 1



We envisioned reaching the tetracyclic complex **2** from an intramolecular [2 + 2 + 2] cyclization of a judiciously substituted allenediyne **3** starting from an already preexisting D ring. This novel strategy would have allowed the creation in one step of the ABC ring system and, most interestingly, the simultaneous introduction of the substituents at both C11 and C10. Subsequent manipulation of **2** might lead to the 11β-aryl corticosteroids **1**.

We previously reported that the cobalt-mediated [2 + 2 + 2] cycloaddition of allenediynes bearing the allene moiety at the terminal position is a completely regio-, chemo-, diastereoselective high-yielding process and one that can be performed with a total transfer of chirality.[10] However, under the same conditions, the allenediyne **4a**, having a tetrasubstituted internal allene, led to the η^4-complexed tricyclic structures as a 7:3 diastereomeric mixture in moderate yield (42%, see Scheme 2).[10a,b]

Scheme 2[a]



4a, R^1 = Me	R^2 = H	70	**5a, 40%**	30
4b, R^1 = Ph		55	**5b, 60%**	45
4c, R^1 = *p*-CF_3Ph		53	**5c, 65%**	47
4d, R^1 = *p*-MeOPh		61	**5d, 62%**	39
4e, R^1 = Ph, R^2 = OMe		65	**5e, 62%**	35

[a] Conditions: $CpCo(CO)_2$ (1 equiv), xylenes, *hν*, Δ.

Thus, before starting the synthesis of **2**, we initially decided to investigate the behavior of different allenediynes **4b**−**e** bearing an aryl group on the allene and to evaluate the influence of such a substituent on the course of the cyclization. Exposure of **4b**−**e** to a stoichiometric amount of $CpCo(CO)_2$ in refluxing xylenes under irradiation led to the complexed tricyclic compounds **5b**−**e** in 60−65% yield as a nearly 1:1 mixture of *endo*/*exo* diastereomers (Scheme 2).[11]

Several features in these cyclizations are noteworthy: (i) they are totally regioselective and lead only to the (6,6,6)-tricyclic cycloadducts; (ii) the yields are higher compared to the cyclization of **4a** due to an increase in the stability of the isolated complexes since they could be purified with nondegassed solvents on silica gel; (iii) the *endo*/*exo* diastereoselectivity is independent of the substitution on the allene; (iv) the cyclization is compatible with an oxyfunctionality at C3.

Since an aryl group was compatible with the conditions of the cyclization, we undertook the synthesis of **3b** (R = H) starting from the commercially available 2-methyl-2-cyclopenten-1-one. Conjugate addition of (trimethylsilyl)-ethynyl copper(I) reagent in the presence of iodotrimethylsilane[12] provided the corresponding silyl enol ether **6** in 95% yield. Subsequent acid hydrolysis furnished the ketone **7** in 85% yield.

Different methods for effecting the alkylation of **6** were quite unsuccessful; the use of MeLi or $NaNH_2$ in THF /HMPA resulted in decomposition of the starting material, whereas the use of NaH led to a complex mixture of the ketone **7** and mono- and trialkylated adducts albeit in low yields (10−12%). The expected alkylated adduct was obtained from **6** with a slightly modified Nicholas reaction[13] (Scheme 3).

Indeed the following sequence (addition of **6** at room temperature to a solution of (propargyl)dicobalt hexacarbonyl cation, demetalation,[14] and acetalization[15] of the corresponding adducts) furnished a 2:1 mixture of the ketals **10*cis*/*trans***. The cis relationship between the alkynyl and ethynyl chain for the major diastereomer was assigned by NOE NMR experiments. Alkylation of the lithium acetylide of **10*cis*/*trans*** with 8-trimethylsilyl-oct-7-yn-2-one provided the corresponding alcohols **11*cis*/*trans*** in 66 and 50% yield, respectively. Almost all attempts at generating the allenes

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(11) *endo*/*exo* stereochemical assigments and ratio were determined by ^{1}H NMR on the basis of the chemical shift and integration of the angular CH_3 (δCH_3 *endo* = 1.80 ppm; δCH_3 *exo* = 1.20 ppm), Cp− and dienic protons, see ref 9b, and for parent compounds: Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 1564−1573.

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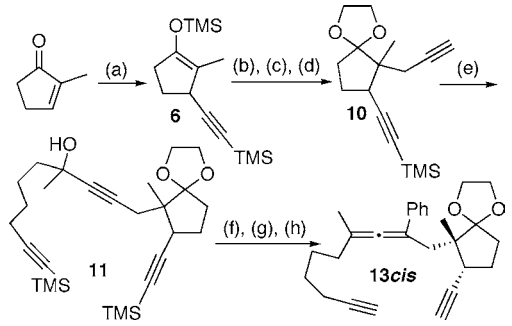
(15) The reaction proceeded in excellent yield only if the following conditions are respected: 10^{-2} M in benzene, 5% PTSA, and 2 equiv of ethylene glycol.

Scheme 3[a]



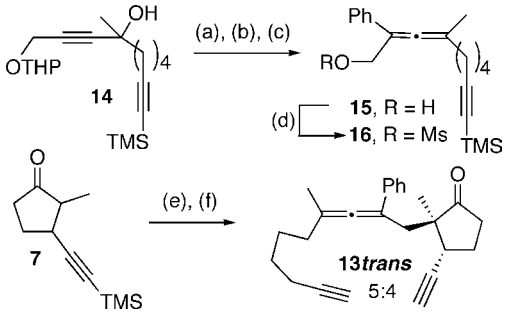
[a] Conditions: (a) *n*-BuLi, $Me_3SiC{\equiv}CH$, TMSI, CuI, THF, −78° to −30 °C, **95%**. (b) $MeOCH_2{-}C{\equiv}CH{\cdot}o_2(CO)_6$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, **95%**. (c) CAN, acetone, rt, **78%**. (d) 5 mol % PTSA, ethylene glycol (2 equiv), benzene (0.01 M), **10*cis/trans***: **95%**. (e) *n*-BuLi, −78 °C, THF, $CH_3C(O)(CH_2)_4C{\equiv}CSiMe_3$, **11*cis***: **60%**; **11*trans***: **50%**. (f) *n*-BuLi; MsCl, THF, −78 °C. (g) $CuBr{\cdot}SMe_2$, PhMgCl, LiBr, THF, −50 °C, **10%**. (h) K_2CO_3, MeOH, rt, **13*cis***: **quant**.

through a sequence of mesylation of the alcohols followed by a S_N2' with copper(I) reagents were unsuccessful. Only the addition of phenylcopper(I) reagent [generated from PhMgCl and $CuBr{\cdot}SMe_2$ in the presence of LiBr] on **11*cis*** furnished the corresponding allene in 10% yield, whereas under the same conditions **11*trans*** (or the mesylate) was recovered. Subsequent quantitative deprotection of the triple bonds afforded the allenediyne **13*cis***. Since the allene formation occurred only for the cis adduct in poor yield, we decided to study another synthetic path to the allene **13**. As alkylation of the ketone **7** with propargyl bromide furnished the corresponding adduct in 60% yield, we checked the feasibility of such an alkylation with the mesylate **16** derived from the alcohol **15**.

The starting material of this sequence was the alcohol **14**, which was generated from the condensation of the lithium derivative of the tetrahydropyranyl propargyl ether with 8-trimethylsilyl-oct-7-yn-2-one. Smooth formation of the allene and acid hydrolysis of the ether provided the alcohol **15** in 94% overall yield. The addition of the corresponding mesylate **16** to the potassium enolate of **7** afforded, after desilylation of the triple bonds, the allenediyne **13*trans*** as a 5:4 mixture of two diastereomers in 50% yield over the three steps (mesylation, alkylation, desilylation). The assigned stereochemistry of the major **13*trans***, which was obtained pure after flash chromatography and crystallization, was unambiguously established by X-ray analysis.[16] In addition, NMR experiments showed also the trans relationship between the two unsaturated chains for the minor **13*trans*** diastereomer.

The cobalt(I)-mediated cyclizations were carried out in the presence of a stoichiometric amount of η^5-cyclopentadienyldicarbonyl cobalt(I) [$CpCo(CO)_2$] in boiling xylenes under

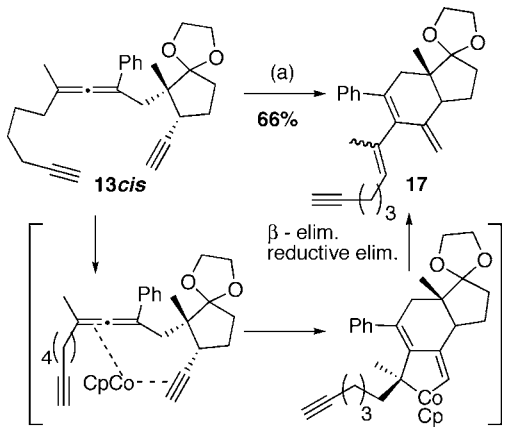
Scheme 4[a]



[a] Conditions: (a) *n*-BuLi, MsCl, THF, −78 °C. (b) $CuBr{\cdot}SMe_2$, PhMgBr, LiBr, −50 °C. (c) cat PTSA, MeOH, rt. (d) Et_3N, cat 4-DMAP, MsCl, CH_2Cl_2, −40 °C. (e) KHMDS, −15 °C, THF; −50 °C, **16**, THF. (f) K_2CO_3, MeOH.

irradiation (300W visible lamp, 50% of its power). Surprisingly, after 20 min, the allenediyne **13*cis*** afforded the bicyclic yne-trienic compound **17** in 66% yield,[17] which could result from a formal Alder ene reaction between the triple bond attached to the five-membered ring and the double bond of the allene bearing the methyl group (Scheme 5).

Scheme 5[a]



[a] Conditions: (a) $CpCo(CO)_2$ (1 equiv), xylenes, *hν*, Δ.

Such an Alder ene reaction has already been observed by our group with some allenediynes and allenynes[18] and occurs competitively with the [2 + 2 + 2] cyclization when the latter is disfavored usually for geometric reasons. In the case of **13*cis***, molecular models showed that the allene and the triple bond are quite close to each other and allow the complexation of these two unsaturations with the cobalt moiety. After oxidative coupling, *β*-elimination followed by reductive elimination furnish the cycloadduct **17**.

On the contrary, when the major diastereomer **13*trans*** was exposed to $CpCo(CO)_2$ in the same conditions as above, we

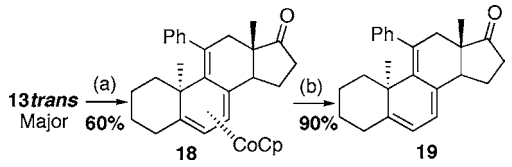
(16) Crystal structures have been deposited at the Cambridge Crystallographic Data Centre with the following deposition numbers: **13*trans***: CCDC 245955; **18**: CCDC 245954. See Supporting Information for the ORTEP representation of major **13 *trans***.

(17) **17** is obtained as a mixture of isomers and is quite unstable.

(18) (a) Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027−7030. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834.

were very pleased to observe the formation of the η^4-cobalt-complexed tetracyclic compound **18** in 60% yield as a single diastereomer that crystallizes from a mixture of pentane/CH_2Cl_2 (Scheme 6).

Scheme 6[a]



[a] Conditions: (a) $CpCo(CO)_2$ (1 equiv), xylenes, *hν*, Δ. (b) SiO_2, CH_2Cl_2, rt.

The free ligand **19** can be easily obtained in 90% yield by a simple treatment of the complex with silica gel in dichloromethane. Therefore, the cyclization/decomplexation sequence can also be carried out without purifying the complex **18** and allowed the formation of the 11-aryl steroid framework in 48% overall yield.

On the basis of the ^{1}H NMR spectrum, the cis relationship between the cobalt moiety and the A/B angular methyl was established (δ = 1.75 ppm). The assigned structure was secured by a single-crystal X-ray analysis.[16] The ORTEP representation (Figure 1) showed, in addition to the *endo* stereochemistry of the complex, the trans relationship between the two angular methyl groups and the nonconjugation of the phenyl group with the Δ_{9-11} double bond

In summary, depending on the stereochemical relationship (cis or trans) between the ethynyl group and the allene, we have noticed two different trends occurring in the cobalt(I)-mediated cyclization of allenediynes that incorporate a five-membered ring. Indeed, we have been able to build the 11-aryl steroid skeleton in 48% yield from the allenediyne

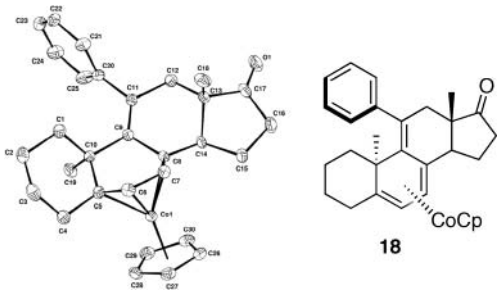


Figure 1.

13*trans*. This new synthetic route highlights the high performance of the cobalt(I)-mediated cycloadditions in the synthesis of complex polycyclic molecules. Further manipulations either of the complex **18** or the free ligand **19**, especially the reduction of the double-bond Δ_{9-11}, are currently being investigated. As we have already observed both the compatibility of an oxy-functionality at C3 and the transfer of axial chirality to a centered one,[10c] the access to compound **2** in an enantiomerically pure form should be straightforward. On the contrary, we have observed another behavior for the allenediyne **13*cis***. Probably because of geometrical restrictions, a formal Alder ene reaction that is competitive to the [2 + 2 + 2] cyclization becomes the major process and leads to a bicyclic yne-trienic compound.

Acknowledgment. M.M. is a member of IUF. Financial support was provided by CNRS, MRES, and IUF. M.P. thanks Aventis−CNRS for his fellowship.

Supporting Information Available: Experimental procedures and characterization data of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0485060