Pergamon

Tetrahedron Letters 43 (2002) 727–730

TETRAHEDRON LETTERS

The intramolecular nucleophilic 1,5-*O*-heterocyclization of (η^4-dienyl)-tricarbonyliron diols: conformationally locked phosphocholines

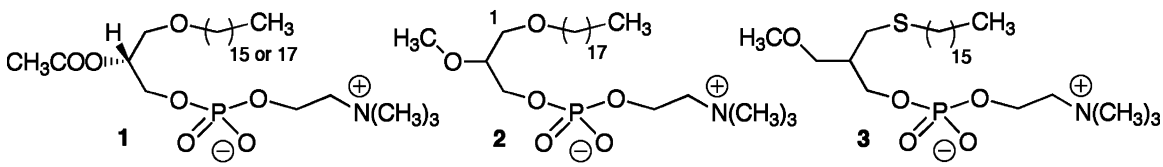
Alain Braun[a] and Jean-Paul Lellouche[b,*]

[a]*CEA, CE-Saclay, DBCM, Service des Molécules Marquées, Bât 547, F-91191 Gif-sur-Yvette, France*
[b]*Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel*

Received 20 June 2001; revised 15 November 2001; accepted 23 November 2001

Abstract—The 1,5-nucleophilic intramolecular *O*-heterocyclization of ψ-*exo*-/ψ-*endo*-(η^4-dienyl)tricarbonyliron diols occurs under acid catalysis with a 1,2-migration of the complexation site. This cyclization proved to be stereoselective and provided a synthetically useful entry to novel conformationally locked alkylphosphocholines as potential anticancer agents. © 2002 Published by Elsevier Science Ltd.

The potent anticancer action of the pro-inflammatory endogenous mediator Paf-Acether **1** raised a lot of interest recently in the synthesis and pharmacological screening of numerous antitumor alkylphospholipids.[1] Among them, *rac*-edelfosine **2** and *rac*-ilmofosine **3** soon appeared as the most potent compounds, not only active in vitro but also in vivo.[1]



These compounds selectively accumulate in the membranes of tumor cells perturbing membrane-localized vital enzymic processes. However, in spite of numerous efforts, the molecular basis of this selective accumulation remained elusive until now. Interestingly, these phosphocholines are based on a conformationally mobile glycerol skeleton. Novel alkylphosphocholines, which will be constrained conformationally, could find useful applications as locked structural probes to understand more rationally their crucial mechanism of action.

The main purposes of this letter are (1) to describe our design of conformationally locked phosphocholines of type **4** with potential anticancer properties (Fig. 1); (2) to demonstrate that an innovative intramolecular nucleophilic 1,5-*O*-heterocyclization of (η^4-dienyl)tricarbonyliron diols **7** is the key stereoselective step for their syntheses; (3) to prove clearly that the *O*-heterocyclization affords optically active derivatives when involving homochiral precursors, and finally; (4) to emphasize the synthetic equivalency of the ester aldehyde diene–$Fe(CO)_3$ complex **8** with the 3*C*-homochiral monofunctional 2,3-dicationic synthon **9**.

We envisioned that the 2-methoxy group of *rac*-edelfosine **2** can be linked to the C(1) of the glycerol backbone to afford conformationally locked phosphocholines of type **4** containing a 2,3-disubstituted dioxane heterocycle (Fig. 1). Phosphocholines of type **4**, where X=O and $n=15$, contain an added methylene inserted into the C(1)–O bond of **2** to improve metabolic stability. Additionally, the dioxane moiety should also provide enzymic stability toward phospholipases C and D. Retrosynthetically, disconnection of the phosphocholine residue in **4** (O–P linkage) reveals the hydroxymethylated-2,3-disubstituted dioxane **5**. The hydroxymethyl

Keywords: anticancer alkylphospholipids; (η^5-dienyl)tricarbonyliron(+1) cations; intramolecular *O*-heterocyclization; 1,5-nucleophilic substitution.

* Corresponding author. Tel.: 972-3-531 83 24; fax: 972-3-535 12 50; e-mail: lellouj@mail.biu.ac.il

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(01)02245-6

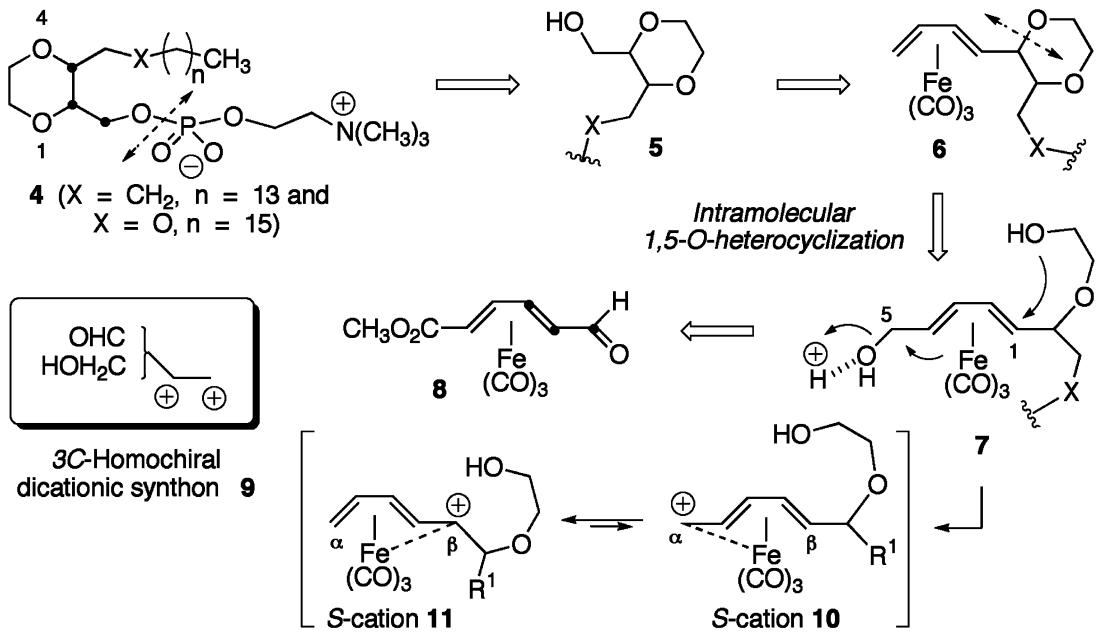
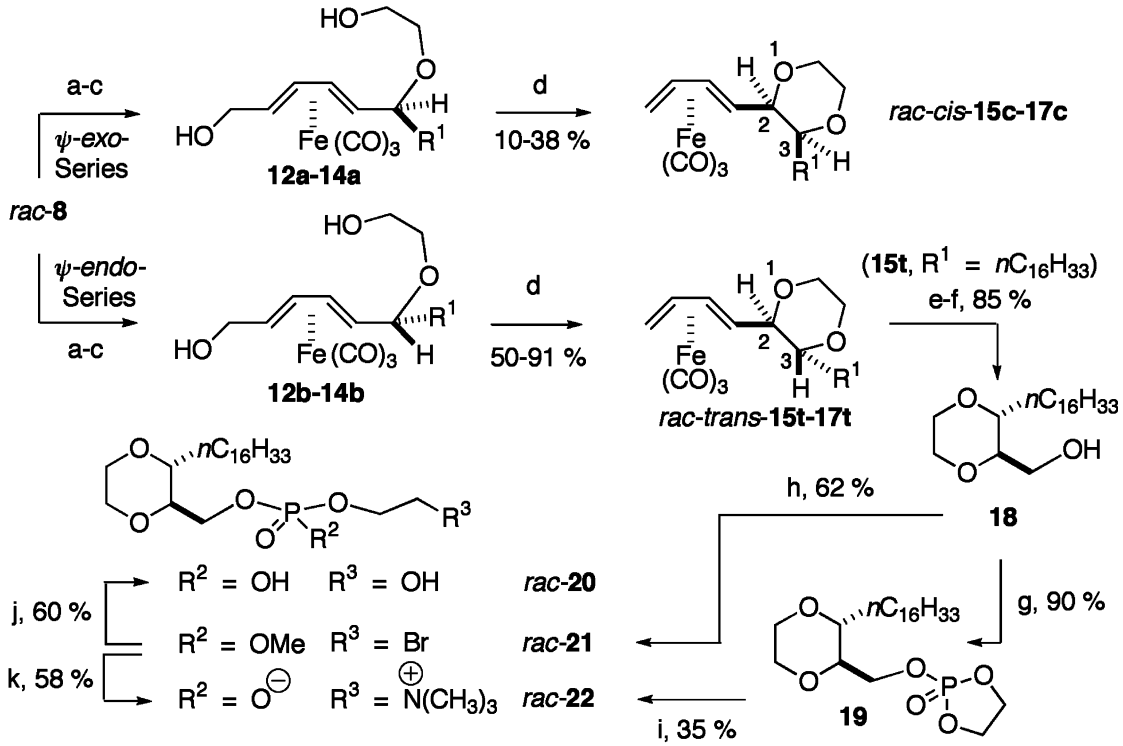


Figure 1.

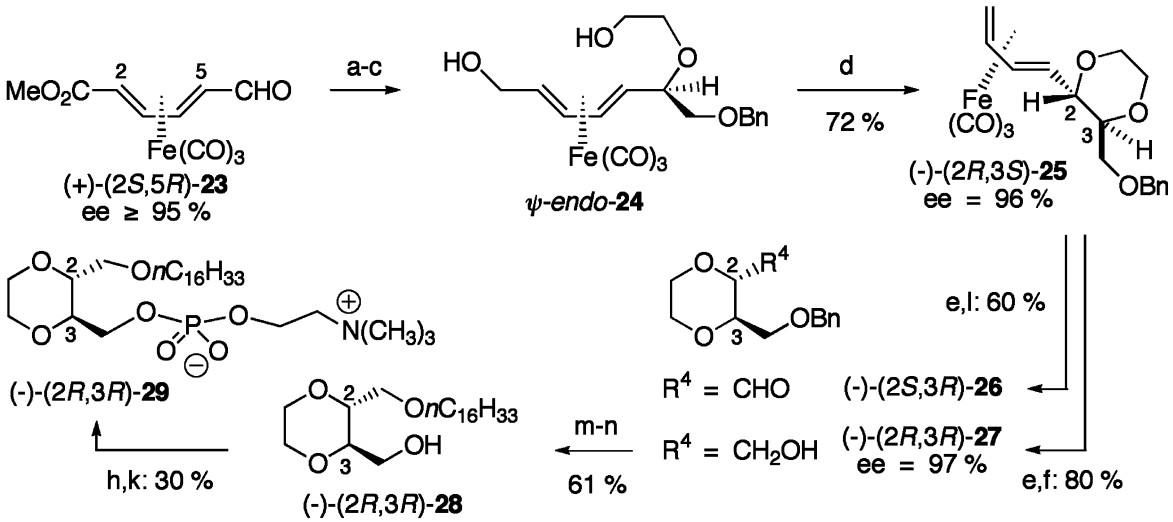
itself can arise from the oxidative treatment of a monosubstituted (1,3-dienyl)-$Fe(CO)_3$ residue present in the *monosubstituted* tricarbonyliron complex **6**. Disconnecting further the critical C–O ether bond close to the $Fe(CO)_3$ moiety unravels the *disubstituted* (η^4-dienyl)tricarbonyliron diol **7** as its logical precursor. In turn, this diol should cyclize via an original acid-catalyzed intramolecular 1,5-*O*-heterocyclization as the key step of our retrosynthesis. As described later, uneventful chemistry can be used to transform the dienyl-$Fe(CO)_3$-ester aldehyde **8** into the required diol **7**.

This retrosynthesis emphasizes nicely the well-known protecting and/or stereodirecting properties associated with the complexing $Fe(CO)_3$ unit as well as the strong stabilization by anchimeric assistance of carbocations close to the coordination site.[2] Concerning the specific key step of *O*-heterocyclization, worthy of mention are the in situ generation of the transoid cation (*S*)-**10** from **7** under acid-catalyzed dehydration (electronic deficiency at *C*α) and isomerization of the complexation site by 1,2-migration of the $Fe(CO)_3$ unit, thus revealing the more stable secondary electrophilic center at *C*β trapped in situ by the pendant tethered OH-nucleophile.[3] Indeed, previous results showed that racemic diastereoisomeric disubstituted dienyl-$Fe(CO)_3$ diols ψ-*exo*-/ψ-*endo*-**12a**–**14a**/**12b**–**14b**[4] (Scheme 1, **12a**/**b**: $R^1 = nC_{16}H_{33}$, **13a**/**b**: $R^1 = CH_2Cl$, **14a**/**b**: $R^1 = CH_2OBn$) prepared from *rac*-**8** in three steps (a–c) can be selectively cyclized using Amberlyst resin (H^+ form) to give ψ-*exo*-*cis*-/ψ-*exo*-*trans*-2,3-disubstituted dioxanes **15c**–**17c**/**15t**–**17t** (step d: CH_2Cl_2, 20°C, 3–12 h, **15c**–**17c**: 10–38%, **15t**–**17t**: 50–91%), respectively.[2d,3,5,6] $^1H/^{13}C$ NMR data of the cyclized monosubstituted iron complexed adducts and crystallographic structures obtained for *rac*-*cis*- and *trans*-**17c**/**17t** ($R^1 = CH_2OBn$) supported the described structures and, more particularly, the ψ-*exo*-diastereoisomeric relationship of the newly formed C(2)–O(1) bond versus the $Fe(CO)_3$ unit (*anti* nucleophilic attack).[3] Further chemical processing of *rac*-**15t** ($R^1 = nC_{16}H_{33}$) to the two targeted racemic phosphocholines *rac*-**20**/*rac*-**22** has been performed in the following manner. Its oxidative decomplexation affords the corresponding *trans*-dioxane diene (step e: $Ce(NH_3)_4(NO_3)_6$, EtOH/AcOEt 2/1, –20°C, 87%), which is ozonized leading to the *trans*-dioxane alcohol *rac*-**18** after an ozonide reductive quench by $NaBH_4$ (steps e–f: combined yield 85%). Introduction of the phosphocholine moiety into *rac*-**18** toward the phospholipid *rac*-**22** can be performed with a similar global efficiency using the two synthetic methodologies of (1) Hirt[7] or of (2) Thuong[8] (32–36% combined yield after preparative HPLC purification, VYDAC-C8 reverse-phase column, solvent A/B 3/2, solvent A: CH_3COCH_3/MeOH/THF/CH_3CO_2H 700/250/50/50, solvent B: H_2O containing 5% CH_3CO_2H, $t_r = 8.5$ min, 1.5 ml/min, He gas-operated DEDL-light diffusion detector, purity ≥ 99%). The first step involves the intermediate brominated phosphate *rac*-**21**, while the second one makes use of the cyclic 1,3,2-dioxaphospholane *rac*-**19**, respectively. In each case, NMe_3 quaternization terminates the synthetic sequence (steps h and k: 36% combined yield; steps g and i: 32% combined yield). Additionally, the chemoselective basic hydrolysis of *rac*-**21** afforded the unsymmetrical phosphate diester *rac*-**20** (step j: NaOH, DME/H_2O 1/1, 20°C, 60%) useful for biological evaluation.

We also demonstrated that the key intramolecular 1,5-*O*-heterocyclization of complexed diols **7** can lead to optically active derivatives when involving homochiral tricarbonyliron complexed diol precursors (Scheme 2). The synthesis of the optically active (–)-(2*R*,3*R*) *trans*-phosphocholine **29** starts from the known resolved complexed ester aldehyde (+)-(2*S*,5*R*)-**23** (ee ≥ 95%),[10]



Scheme 1. *Reagents and conditions*: (a) R^1Li or R^1MgBr, THF, −78°C, 1 h, 77–97% (chromatographic separation of ψ-*exo*/ψ-*endo*-diastereoisomers ~3/1); (b) N_2CHCO_2Et, cat. $[Rh_2(OAc)_4]$, CH_2Cl_2, 20°C, 1 h, 46–80%; (c) DIBAL-H, CH_2Cl_2, −78°C, 1 h, 63–82%; (d) Amberlyst™ resin (acid form), CH_2Cl_2, 20°C, 3–12 h; (e) $Ce(NH_3)_4(NO_3)_6$, EtOH/AcOEt 2/1, −20°C, 0.5 h, 87%; (f) O_3, Et_2O, −78°C, 0.5 h; $NaBH_4$, EtOH, 0°C, 1 h, 98%; (g) 2-chloro-1-[1,3,2]-dioxaphospholane 2-oxide, Ph, Et_3N, 20°C, 2 h; (h) 2-bromoethylphosphorodichloridate, Ph, Et_3N, 20°C, 2 h, MeOH quench; (i) NMe_3, PhMe, reflux, 2 h; (j) NaOH, DME/H_2O 1/1, 20°C, 4 h; (k) NMe_3, PhMe, 20°C, 24 h.



Scheme 2. *Reagents and conditions*: Steps a–f, h and k (Scheme 1); (a) $BnOCH_2Li$,[9] THF, 0°C, 0.25 h, 97% (chromatographic separation of ψ-*exo*/ψ-*endo*-diastereoisomers ~65/35); (b) 50%; (c) 63%; (d) 72%; (e) 92%; (f) 87%; (h) 58%; (k) 50%; (l) O_3, Et_2O, −78°C, 0.25 h, Me_2S quench, 65%; (m) NaH, DMF/HMPT 95/5, 20°C, 6 h, 66%; (n) H_2, Raney Ni, EtOH, 20°C, 24 h, 92%.

which is submitted to similar steps a–c toward the ψ-*endo*-diol **24**.

The diol **24** affords the (−)-(2*R*,3*S*)-*trans*-dioxane complex **25** in a similar global yield of 8% from (+)-(2*S*,5*R*)-**23** after Amberlyst™ resin (H^+ form)-catalyzed *O*-heterocyclization. Removal of paramagnetic impurities from the crude compound (silica gel pad, ether) followed by high-field NMR analyses did not allow us to detect any other diastereoisomer besides **25** ($^1H/^{13}C$

NMR, 300 MHz, $CDCl_3$ and C_6D_6, diastereoisomeric purity $\geq 98\%$). Moreover, the optical purity of (−)-(2*R*,3*S*)-**25** has been assayed to be 96% by chiral HPLC using a Chiracel OD column eluted by the mixture *n*-hexane/isopropanol 95/5 (0.8 ml/min, $t_r = 12.5$ min, $\lambda_{UV} = 230$ nm). Under the same conditions, the racemic compound *rac-trans*-**17t** (Scheme 1, $R^1 = CH_2OBn$) is perfectly resolved into two baseline-separated picks eluted at 7.0 and 12.5 min. *To the best of our knowledge, this cationic cyclization of dienyl-Fe(CO)$_3$ diols is a unique case of stereoselective intramolecular 1,5-O-heterocyclization occurring with migration of the site of complexation.*[5] With (−)-(2*R*,3*S*)-**25** at hand, the optically active phospholipid (−)-(2*R*,3*R*)-**29** can be prepared uneventfully (Scheme 2) including some minor synthetic variations of Scheme 1. Worthy of note are (1) the preparation of the diversely functionalized (−)-(2*S*,3*S*)-*trans*-**26**, which opens an easy access to structurally different phosphocholines, and (2) the optical purity of the monobenzylated (−)-(2*R*,3*R*)-*trans*-**27** better than 97% as measured under the same conditions as for (−)-(2*R*,3*S*)-**25** (0.8 ml/min, $t_r = 10.5$ min, $\lambda_{UV} = 230$ nm).

In conclusion, the acid-catalyzed intramolecular 1,5-*O*-heterocyclization of (η^4-dienyl)tricarbonyliron diols has been shown to be a key stereoselective step towards racemic and optically active conformationally locked phosphocholines. Accordingly, the starting complex (+)-(2*S*,5*R*)-**23** can be viewed as a 3*C*-homochiral functional dicationic synthon of type **9** (Fig. 1).[11]

Acknowledgements

The authors are grateful to Drs. Yves Rolland, René Grée and Charles Mioskowski for their interest during this work. A.B. thanks the Servier Institute (Suresnes) for its financial support through a research fellowship.

References

1. (a) Berkovic, D. *Gen. Pharmacol.* **1998**, *31*, 511–517; (b) Arthur, G.; Bittman, R. *Biochim. Biophys. Acta* **1998**, *1390*, 85–102.
2. (a) Koerner Von Gustorf, E. A.; Grevels, F. W.; Fisher, I. In *The Organic Chemistry of Iron*; Koerner Von Gustorf, E. A.; Grevels, F. W.; Fisher, I., Eds.; Academic Press: New York, 1978; Vols. I–II; (b) Pearson, A. J. In *Metallo-Organic Chemistry*; John Wiley and Sons: New York, 1985; (c) Grée, R. *Synthesis* **1989**, 341–355; (d) Grée, R.; Lellouche, J.-P. *Advances in Metal-Organic Chemistry*; Acyclic diene tricarbonyliron complexes in organic synthesis, 1993; Vol. 4, pp. 1–166.
3. Braun, A.; Lellouche, J.-P. *J. Org. Chem.* **1996**, *61*, 1914–1915 and references cited therein.
4. Clinton, N. A.; Lyllia, C. P. *J. Am. Chem. Soc.* **1970**, *92*, 3058–3064.
5. Similarly *but in a bimolecular way* (η^4-dienyl)tricarbonyliron complexed *O*-acyl/phosphoryl-cyanohydrins have been shown to react with various heteronucleophiles affording 1,2-migration adducts of the $Fe(CO)_3$ moiety: Takemoto, Y.; Yoshikawa, N.; Baba, Y.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H. *J. Am. Chem. Soc.* **1999**, *121*, 9143–9154 and references cited therein.
6. Various iron complexed chiral non-racemic heterocycles have been obtained but without migration of the site of complexation: see 2(d) and (a) Grée, D. M.; Martelli, J. T.; Grée, R. *J. Org. Chem.* **1995**, *60*, 2316–2317; (b) Hachem, A.; Toupet, L.; Grée, R. *Tetrahedron Lett.* **1995**, *36*, 1849–1852; (c) Ripoche, I.; Gelas, J.; Grée, D.; Grée, R.; Troin, Y. *Tetrahedron Lett.* **1995**, *36*, 6675–6678.
7. Hirt, R.; Berchtold, R. *Pharm. Acta Helv.* **1958**, *33*, 349–356.
8. Thuong, N. T.; Charbier, P. *Bull. Soc. Chim. Fr.* **1974**, *3–4*, 667–671.
9. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.
10. Monpert, A.; Martelli, J.; Grée, R.; Carrié, R. *Tetrahedron Lett.* **1981**, *22*, 1961–1964.
11. The new compounds have been fully characterized (microanalyses, TLC and/or HPLC, FT-IR, high-field $^1H/^{13}C$ NMR, EI/DCI-MS).