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Symmetrically-substituted decalin-based scaffolds

Zoi F. Plyta,[a] Eberhard Heller,[a] Françoise Dumas,[a,*] Christine Miet,[a] Jacqueline Mahuteau,[a] Jean d'Angelo,[a,*] Juan Caturla [b] and Marie-Elise Tran Huu Dau [c]

[a]*Centre d'Etudes Pharmaceutiques, Université de Paris Sud, Laboratoire de Synthèse Organique, BIOCIS, Unité associée au CNRS 5, rue J.-B. Clément, 92296 Châtenay-Malabry, France*

[b]*Philipps-Universität Marburg, Fachbereich Chemie, 35032, Marburg, Germany*

[c]*Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif sur Yvette, France*

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Abstract

The synthesis of a chiral scaffold was achieved by coupling a decalintriol platform with a NH-Boc protected α-ethylenic γ-amino acid. The two side chains of this molecule strongly self-associate through intramolecular hydrogen bonding involving the NH-Boc residues.

Keywords: conformation; hydrogen bonding; molecular modeling; molecular recognition; NMR.

Important progress has been made in synthesizing catalytic systems for asymmetric recognition.[1–3] As learned from the chemistry of enzymes, selective catalysis may be achieved through the cooperative action of functional groups which converge on a substrate positioned centrally in an 'active site'. The catalytic/binding units can be located separately on a rigid platform, such that they can surround a substrate molecule with an array of convergent functionality. Furthermore, since it is desirable to design molecular catalysts as heterogeneous systems viable through many cycles of reuse, the scaffold should require a further anchor point through which it can be connected to a polymer support. The aim of this paper was to elaborate new scaffolds in which two *identical* chiral chains, at a separation distance of approximately 5 Å, protrude orthogonally to the same face of a rigid framework. It was our hope that such a topology forces the two chains to converge and to act as a part of an 'active site', featuring an asymmetric microenvironment. An advantage offered by the presence of two identical side chains is that, provided they satisfy definite structural requirements (vide infra the criteria of selection of **6**), they would cooperate within this 'active site' as chiral ligands of virtual C_2-symmetry.

We reasoned that *trans*-fused decalintriol **4** may constitute an attractive, simple *meso* tripodal platform, so that the introduction of two identical chiral legs through esterification of the *axial* secondary alcohol groups at C-2 and C-7 could afford the desired chiral scaffold, the angular hydroxymethyl group at C-4a ensuring a site of attachment to the polymer matrix. We report here such a structure (**7**). As evidenced by

* Corresponding authors. E-mail: jean.dangelo@cep.u-psud.fr (J. d'Angelo)

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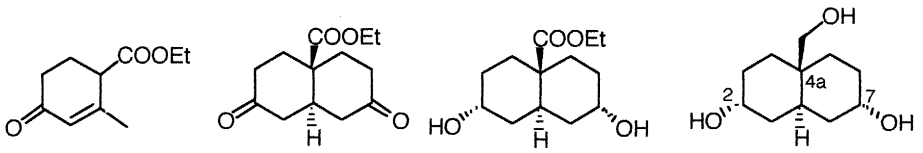
IR and NMR spectroscopy, and complemented by computer modeling studies, the two chiral appendages of this molecule strongly self-associate through intramolecular hydrogen bonding involving the NH-Boc residues. *trans*-2,7-Decalindione **2**, precursor of triol **4**, was prepared in three steps, according to the methodology of Jones, starting from Hagemann's ester **1**.[4] Stereoselective reduction of **2** with K-Selectride® (1 h at −45°C in THF) gave *meso* diol **3** with a 96% yield. The *cis*-diaxial relationship between the two hydroxyl groups in **3** was unequivocally assigned by 400 MHz ^{1}H NMR spectroscopy. The two *equatorial* protons at C-2 and C-7 indeed appeared as a unique multiplet exhibiting coupling constants of ca. 3 Hz, centered at 4.10 ppm ($CDCl_3$). Reduction of **3** with lithium aluminum hydride gave key triol **4** (LAH, THF, 16 h at 40°C, 94% yield).



1 **2** **3** **4**

Selective protection of the primary alcohol function of **4** with a *tert*-butyldiphenylsilyl group then furnished diol **5** (*t*-BuPh_2SiCl, pyridine, DMF, 45 h at 20°C, 40% conversion, 85% yield). The present choice of *N*-Boc-protected α-ethylenic-γ-amino acid (*S*,*E*)-**6**[5] as chiral chain to be linked with platform **5** was guided by the following considerations: (a) the terminal NH-Boc group is a latent basic amine functionality for the recognition of a substrate within the 'active site'; (b) the presence of a double bond prevents the foldback of the chain; (c) owing to the $A^{(1,3)}$-strain induced by the vinylic methyl group, the chain is conformationally constrained; and (d) one would expect no significant interaction of the stereogenic centers present in the side chains with the decalin unit in target scaffold **7**, because they are separated from this platform by four atom-spacers of restricted flexibility; on the other hand, assuming that the tethered chains tend to converge, these peripheral stereocenters might cooperate and dictate the chirality within the 'active site'.

Synthesis of scaffold **7** was achieved by coupling diol **5** with 2 equiv. of acid **6** (DCC, cat. DMAP, THF, 30 h at 40°C, 50% yield). HPLC analysis of **7** discriminated three species, the ratio of which depending on the nature of the solvent and the age of the sample (Fig. 1). The 400 MHz ^{1}H NMR spectrum of compound **7** in $CDCl_3$ showed the presence of three hydrogen-bonded conformers in the ratio of ca. 4:2:1. That the equilibration between these conformers is slow relative to the NMR time scale was revealed by the splitting of resonances into triads centered, respectively, at 6.58, 6.48 and 6.44 ppm (vinylic protons), 5.18, 5.07 and 5.03 ppm (H-2 and H-7 protons), and 1.95, 1.89 and 1.86 ppm (vinylic methyl protons). Unfortunately, assignment of the NH signals was thwarted by overlapping with other resonances. However, the IR spectrum of **7** clearly disclosed the existence of hydrogen-bonded NH (strong broad band at 3370 cm^{-1}), along with free NH (weak sharp band at 3610 cm^{-1}).

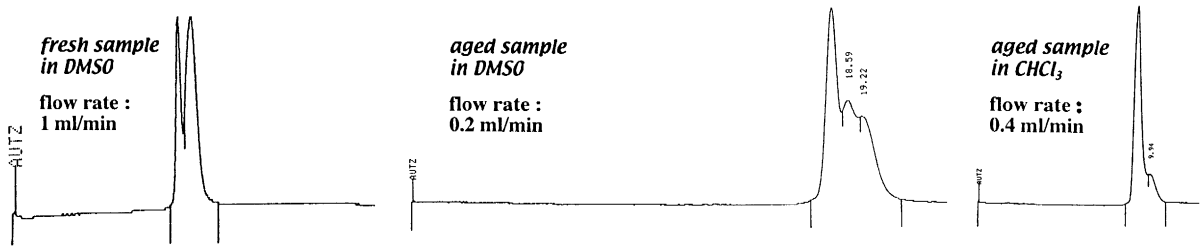
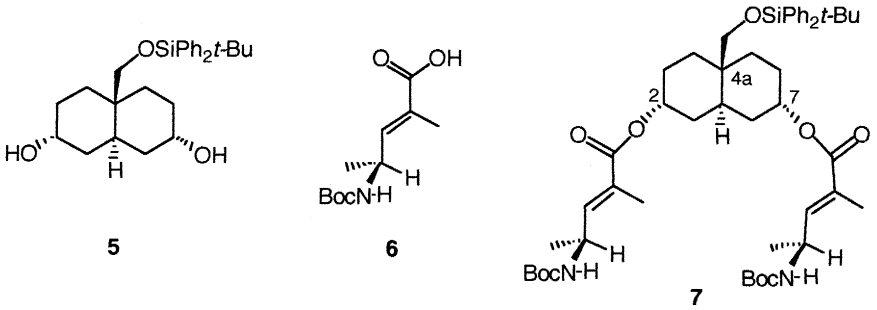


Fig. 1. HPLC analysis of **7** (Spherisorb S5W, length 25 cm, internal diameter 4.9 mm; eluent: AcOEt; detection: UV at 254 nm)



Molecular modeling studies were then undertaken to investigate the ability of the designed scaffold to adopt hydrogen-bonded conformations. For simplicity, the computational studies were performed on an analog to **7**, in which the *tert*-butyldiphenylsilyloxy group was replaced by a methoxy substituent. This structure was subjected to an extensive, unconstrained Monte Carlo/energy minimization conformational search in an implicit chloroform solvatation model.[6] Within 3 kcal/mol of the lowest energy conformation, a population of 15 conformers was identified which *all* are stabilized by intramolecular single or double (cross-strand) hydrogen bonding. It is noteworthy that the latter pattern is reminiscent of the stabilization of the β-hairpin structures encountered in proteins. This marked propensity to form hydrogen bonds reflects the strong self-organization of the bis-carbamate system, in which the NH proton of one of the side chains is positioned to participate in a H bond of ca. 1.9 Å with the carbamoyl oxygen atom of the neighboring chain. The lowest energy conformer **A**, the second lowest energy conformer **B** (+0.9 kcal/mol relative to **A**), and the third one **C** (+1.3 kcal/mol relative to **A**), have populations relative to all conformers of 57%, 13% and 7%, respectively. Two salient structural features characterize this conformer triad: (a) **A** and **B** are both stabilized by a cross-strand hydrogen bonding, whereas a single hydrogen bond is present in **C**; (b) in conformers **A** and **C** the two enoate moieties exist in the *synperiplanar* (*s-cis*) conformation, while in **B** one enoate is *s-cis* and the other one *s-trans* (Fig. 2).

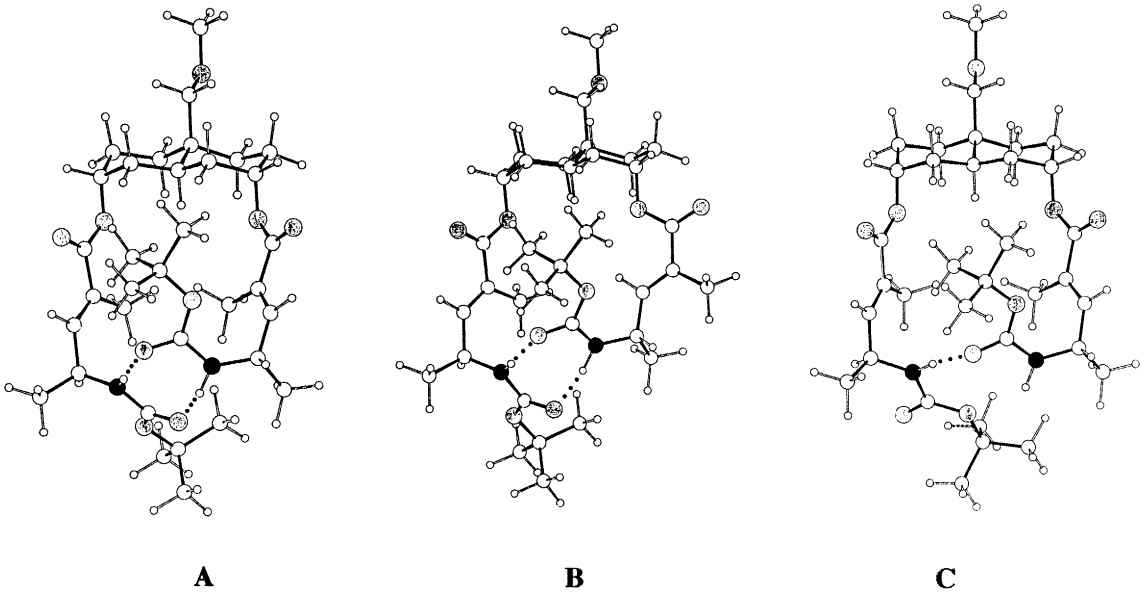
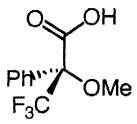


Fig. 2. Computer-based modeling of the 4a-methoxymethyl analog of **7** (H bonds are symbolized by dotted lines)

That the length of the spacers separating the decalin platform from the stereocenters present in the side chains constitutes a decisive factor in designing scaffold **7** was emphasized by synthesizing the

bis-Mosher analog **9** [*i*: (*R*)-MTPA **8**, $NaHCO_3$, H_2O, then drying; *ii*: $(COCl)_2$, benzene; *iii*: 0.3 equiv. of **5**, *N*-(4-pyridyl)pyridine, CCl_4, 48 h at 20°C, 75% yield]. Indeed, since only two atoms separate the stereocenters of the chiral appendages from the decalin nucleus in compound **9**, the interconversion among conformers is now hindered by steric interactions which increase the energy of the rotational barriers (gear effect). This phenomenon was evidenced by the important anisochrony exhibited in ^{1}H, ^{13}C (data not shown), and ^{19}F NMR spectroscopy (in $CDCl_3$, at 298 K): MeO proton resonance split into four main signals centered at 4.29, 4.34, 4.41 and 4.43 ppm; H-2 and H-7 resonances centered at 4.00 and 5.34 ppm; CF_3 fluorine resonance split into four main signals centered at −71.81, −71.69, −71.66 and −71.38 ppm.



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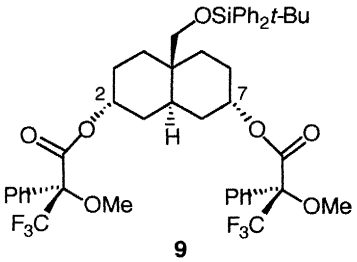

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To conclude, compound **7** represents the prototype of scaffolds in which two identical chiral chains bound to a decalin platform converge to create a chiral site, featuring an ideal microenvironment, e.g. for complexing metal ions.[7,8] Furthermore, such rigid molecules that present functional groups on the same face of the structure can serve as core molecules addressable for combinatorial chemistry.[9] Applications of these scaffolds in asymmetric recognition are currently in progress in our laboratories.

Acknowledgements

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