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Macrolactone-based dynamic combinatorial libraries of cholate monomers bearing recognition functionality

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Abstract

Dynamic combinatorial libraries were generated incorporating new pyridine and dimethylaniline containing monomers. These libraries were analyzed using ^{1}H NMR and HPLC–UV–MS. © 2000 Published by Elsevier Science Ltd.

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In the process of expanding our group's work on templating dynamic combinatorial libraries (DCLs),[1] we have now synthesized monomers **Sp** and **Sd**. The monomers were designed to function as isosteres of the deoxycholic acid monomer **Sa** (Fig. 1) with directional recognition functionality specific for metal centers. We have also devised conditions for the quantitative analysis of libraries.

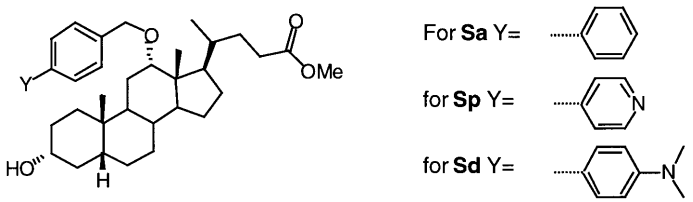

Figure 1. Deoxycholate monomers utilized in DCL formation

In earlier work, when a 5 mM solution of **Sa** in toluene was exposed to the reversible macrolactonization conditions developed for DCL formation, primarily cyclic dimer, trimer and tetramer were formed. The product distribution changed upon addition of alkali metal ions[2] indicating that a template effect was occurring. An ESI-MS study of the interaction between

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alkali metal ions and the individual constituents of these DCLs provided a correlation with the observed product distribution changes.[3]

With this result in hand, we wished to increase the range of templates available to steroidal monomers. Incorporating a pyridyl unit into **Sp** would allow the use of co-ordination chemistry as a more sophisticated templating tool than the essentially directionless electrostatic interactions that operated previously with alkali metal ions. The **Sd** monomer would act as a control in these reactions—this monomer, bearing a tertiary amine, should bind less strongly than the pyridine unit in **Sp** to carefully chosen metal centers.

Synthesis of **Sp** and **Sd** was straightforward (Fig. 2). Acetimidates **1** and **2** were prepared using literature conditions[4] from the corresponding alcohols. Methyl deoxycholate-3′-acetate was reacted under previously developed[2] acid catalyzed conditions with the acetimidate **1** to form **3**. This intermediate was coupled with 4-trimethylstannylpyridine[5] under Stille coupling conditions[6] to form the biaryl compound, which was then deprotected under basic conditions to provide **Sp**.

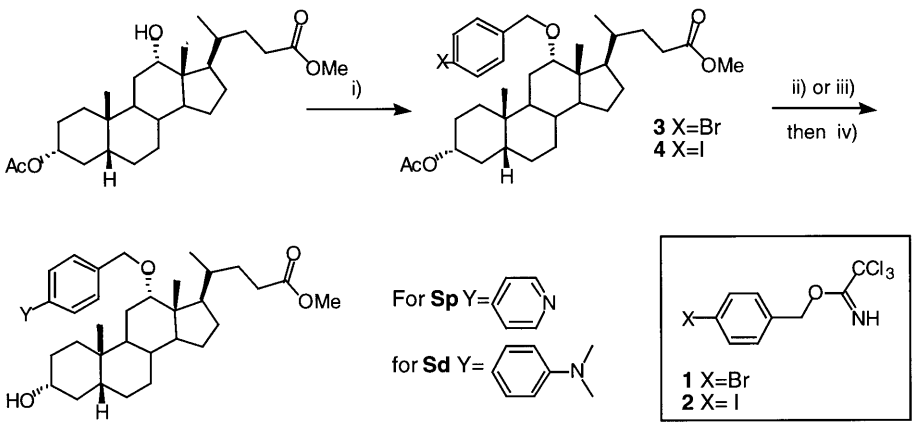

Figure 2. Synthesis of **Sp** and **Sd**. (i) **1** or **2** (1.2 equiv.), CCl_4, C_6H_{12}, F_3CSO_3H (0.05 equiv.), 4 Å molecular sieves, rt, 3 h, 70%; (ii) 4-trimethylstannylpyridine (2 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), toluene, reflux, 48 h, 70%; (iii) 4-(*N*,*N*-dimethylamino) phenylzincbromide (1.1 equiv.), $Pd(PPh_3)_4$ (0.05 equiv.), THF, rt, 2 h, 65%; (iv) KOMe (2 equiv.), MeOH, THF, rt, 1 h, 90%

The analogous Stille reaction was carried out to synthesize **Sd** and this resulted in a product which was extremely laborious to purify. The organozinc compound of 4-bromodimethylaniline[7] also reacted sluggishly under Negishi[8] conditions with **3**. Using iodo intermediate **4** under the same reaction conditions provided the biaryl that was essentially free of contaminants. This intermediate was deprotected under standard conditions to provide **Sd**. All new compounds gave satisfactory ^1H and ^{13}C NMR, IR, HRMS and HPLC analyses.[9]

Cyclization of the monomers at 5 mM utilizing our standard thermodynamic macrolactonization conditions provided DCLs containing >90% dimer, trimer and tetramer, as demonstrated by HPLC–MS and ^1H NMR. Cyclization of **Sp** provided a 40:50:10 ratio of dimer:trimer:tetramer, while **Sd** gave 25:50:25. The decrease in dimer in the case of **Sd** relative to **Sp** was probably caused by repulsion between the electron rich aniline rings, or steric repulsion between the dimethylamine groups.

Individual samples of cyclic species $\mathbf{Sp_2}$, $\mathbf{Sp_3}$, $\mathbf{Sp_4}$, $\mathbf{Sd_2}$, $\mathbf{Sd_3}$ and $\mathbf{Sd_4}$ were separated from DCL reaction mixtures using preparative TLC. The spectroscopic (^1H NMR) and chromatographic

(RP-HPLC) properties of these compounds confirmed the identity of the cyclization components.

Cyclizing a 1:1 mixture of **Sp** and **Sd** at 5 mM total monomer concentration resulted in a DCL containing at least 16 species, as demonstrated by ESI-MS. A ^{1}H NMR spectrum of the DCL at 600 MHz showed a well resolved set of signals corresponding to the 12βH protons in the dimers $\mathbf{Sp_2}$, **SpSd** and $\mathbf{Sd_2}$. Integration of these signals indicated the expected 1:2:1 ratio of these macrocycles. All other 'fingerprint' signals corresponding to other protons in the mixed macrocycles were too closely spaced for accurate integration.

To fully quantitate this DCL, we turned to HPLC. After much experimentation, a reverse phase column (Supelco ABZ^{+} C_{16} alkylamide) was found to give the best separation of DCL components. A two-stage gradient elution was employed utilizing mixtures of MeCN (with 5% aqueous HCO_2H) and ^{i}PrOH (with 5% aqueous HCO_2H). The oligomers were cleanly separated in a 70 minute HPLC run (Fig. 3), and their relative quantities ascertained by integration of the UV absorptions. Individual UV spectra of each peak displayed the expected ratios of maxima at 260 and 290 nm corresponding to the absorptions of the phenylpyridine and phenylaniline ring systems. Additionally, use of ESI-MS allowed examination of each peak's mass spectrum and these were also found to be in accordance with predicted values.

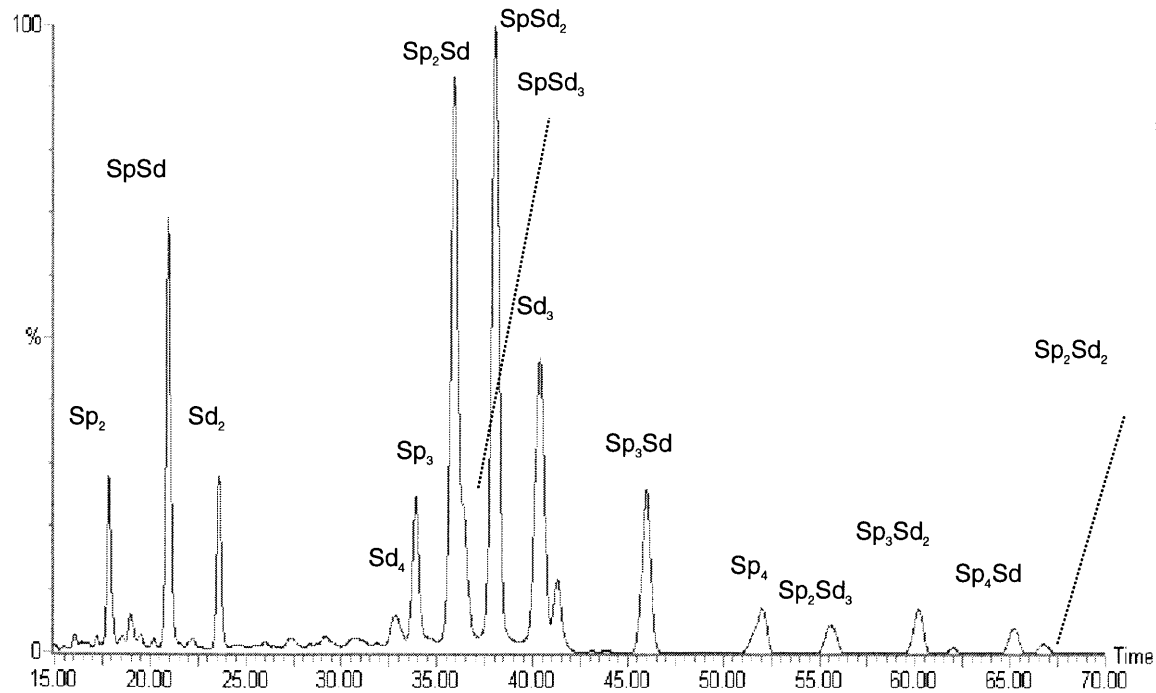

Figure 3. HPLC–MS of the **Sp**+**Sd** DCL

We attempted to template these reactions utilizing coordination to either zinc(II) porphyrins or Pt(II). Complexes of **Sp** with Pt(II) or electron deficient Zn(II) porphyrins such as tetrakis(*meso*-phenyl) octachloroporphyrin and tetrakis(*meso*-trifluoromethyl) porphyrin were synthesized. When these complexes were exposed to our DCL forming conditions no macrolactones were observed and reduction byproducts of the template molecule were formed.

Utilizing the more electron rich Zn(II) tetraphenylporphyrin resulted in competitive binding of the catalyst to the porphyrin and necessitated the addition of excessive amounts of catalyst to drive the reaction to completion. Analysis of these DCLs showed no appreciable shift in the oligomer distributions.

Through these studies it has become clear that the present transesterification reaction conditions severely limit the scope of the molecular recognition chemistries available to template DCLs. Utilization of milder bond-breaking and making chemistry appears to be the key to successful templating of DCLs using complex structures. These studies[10,11] are currently underway.

Supplementary information: HPLC methods and characterizations of monomers/oligomers are available upon request.

Acknowledgements

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Sd monomer. ^{1}H NMR: 7.54 (2H, d, $J=8.1$ Hz, mArH), 7.51 (2H, d, $J=8.7$ Hz, anβH), 7.39 (2H, d, $J=8.1$ Hz, oArH), 6.80 (2H, d, $J=8.7$ Hz, anαH), 4.32–4.61 (2H, ABq, $J=11.6$ Hz, $ArCH_2$), 3.71 (1H, m, 12βH), 3.66 (3H, s, CO_2CH_3), 3.57 (1H, m, 3βH), 2.99 (6H, s, $N(CH_3)_2$). HRMS (+FAB): 601.4130 $(M-CH_2)^+$ $C_{39}H_{55}NO_4$ requires 601.4186.
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