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Synthesis of macrocyclic chromotropic acid-based sulfonamides; their complexation properties and an unexpected photochemical reaction

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ABSTRACT

Chromotropic acid (CTA), a dihydroxynaphthalenedisulfonic acid is a reagent that is widely used for dyestuff manufacture, as a chromogen-forming reagent for the analysis of formaldehyde and as an intermediate for azo derivatives used as analytical reagents. The synthesis of two new CTA-based macrocyclic tetra-sulfonamides **7** and **7a** and their corresponding bis-sulfonamides **10** and **10a** and their complexation properties toward tetra-*n*-butylammonium halides were studied. The X-ray structure of **10a** was determined and it provided key evidence for an unexpected photochemical reaction that the tetra-sulfonamides underwent.

We have been interested in the chemistry of chromotropic acid **1** (4,5-dihydroxy-2,7-naphthalenedisulphonic acid, or 'CTA') for some time now.[1] CTA has been used as a key reagent for the syntheses of various azo derivatives, which can be used not only in the dye industry, but also in a variety of analytical chemistry applications.[2] Eegriwe[3] first described its use in 1937 as a formaldehyde-specific reagent but it was only more recently in 1989 that the mechanism of the chromogen-forming reaction was deciphered.[1] In the same year, Poh et al. showed that the reaction of **2**, the disodium salt of CTA, with formaldehyde in an aqueous solution, in the absence of concentrated sulfuric acid produced a water-soluble cyclic tetramer which he called 'cyclotetrachromotropylene' (**3**) (Scheme 1).[4] This compound which can be considered to be a calixarene analogue, could not, however, be crystallized and was mainly characterized by its mass spectrum. Nevertheless, Poh's group published several papers[5] which revealed that **3** showed typical host-guest properties with various guest species.

We were therefore interested in investigating the potential host–guest properties of macrocyclic CTA-based sulfonamides which could be formed using the diamino compounds, Jeffamines® EDR-148 and EDR-176.[6] The products formed from these diamino compounds with isophthaloyl dichloride were previously studied for their complexation properties with Groups 1 and 2 halides and also with tetrabutylammonium halides (TBAX, where X = Cl, Br, I).[7] As further impetus for our work, Lan et al.[8] had reported the synthesis (Scheme 2) of macrocyclic tetrasulfonamides **4** based upon 3,6-dihydroxy-2,7-naphthalene disulfonic acid, a regioisomer of CTA, via the corresponding 3,6-dimethoxy-disulfonyldichloride (**5**). These authors reported that their compounds were used as good hosts for small solvent molecules such as DMF. Bocheńska et al.[9] reported some other macrocyclic sulfonamides however which were ion-selective ionophores for K^+, Rb^+, and Cs^+.

In this Letter we report the synthesis of four new CTA-based macrocyclic sulfonamides which were conducted in order to evaluate their potential host–guest properties. Some of these properties were evaluated in complexation studies with Groups 1 and 2, and tetrabutylammonium (TBA) halides. As well, the single-crystal X-ray structure of one of these compounds was determined and is reported. During the course of these studies, an unexpected photochemical reaction was observed which is also described herein.

The original macrocyclic sulfonamides which were targeted as shown in Scheme 3, were **6** and **6a** in which the naphthalene rings bear free hydroxyl groups, as in CTA itself. The reaction of the disulfonyldichloride of CTA with 1,8-diamino-3,6-dioxaoctane (**9**, 'Jeffamine® EDR-148')[6] or with 1,10-diamino-4,7-dioxadecane (**9a**, 'Jeffamine® EDR-176') was envisioned as a potential route to **6** and **6a**, respectively. Paruch et al.[10] in 2000 showed that an efficient way to functionalize CTA to its disulfonyldichloride **8**, was to first convert it, via its sodium salt **2**, to the corresponding ditosylate which could then form **8** in good yields. Therefore, this approach was taken by us and after considerable experimentation, conditions were found from which the syntheses of the tosylated macrocycles **7** and **7a** were achieved.

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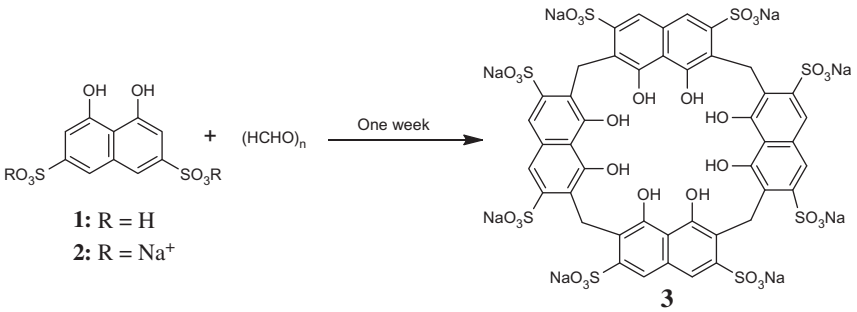
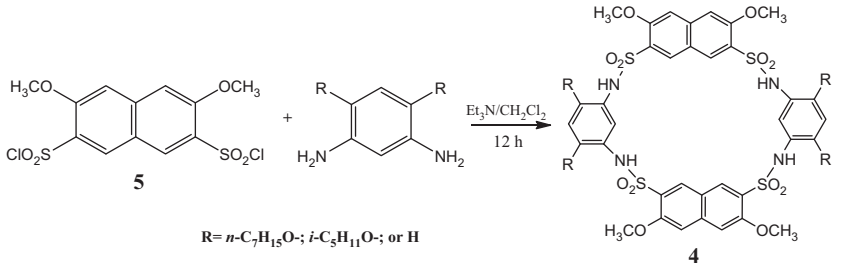


Scheme 1. Poh's synthesis of cyclotetrachromotropylene (**3**).[4]

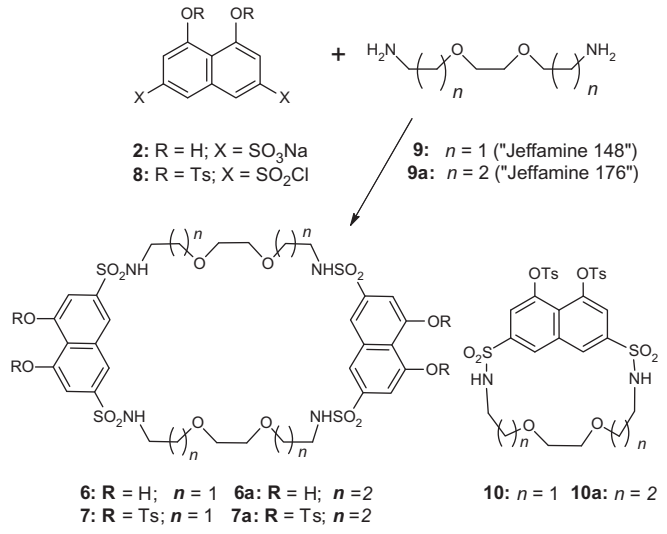


Scheme 2. Lan's synthesis of macrocyclic tetrasulfonamides.[8]

In our initial experiments reacting **8** with **9** with triethylamine, in acetonitrile under high dilution conditions, at either 0 °C or −78 °C afforded only the [1+1] product **10** in 65% yield. However, when dichloromethane was used instead as the solvent, at −100 °C, the desired [2+2] product **7** was formed in 47% yields in a mixture with **10** which was formed in 16% yields. Similarly, reaction of **8** with **9a** in acetonitrile only afforded the corresponding [1+1] product **10a**, in 76% yields. Using dichloromethane instead as the solvent at −100 °C however, formed the desired [2+2] product **7a** in 45% yields in a mixture together with **10a** in 13% yields.

Although Paruch et al.[10] reported being able to de-tosylate their CTA-derived product, all attempts to de-tosylate our compounds only afforded intractable products which could not be characterized. Therefore since it was not possible to produce the free hydroxy group-containing sulfonamides **6** or **6a**, host–guest complexation studies were conducted on all four of the tosylated products instead.

Each of the macrocyles **7**, **7a**, **10,** and **10a** were tested using ^{1}H NMR titration experiments with Groups 1 and 2 chlorides. An analogous study with isophthaloyl macrocyclic amides was previously reported by us.[7] In all cases, in contrast to the findings with the macrocyclic amides, no chemically-induced shifts (CIS) could be observed when solutions of the CTA macrocycles in a 9:1 $CDCl_3$; DMSO-d_6 solvent mixture were saturated with the metal salts. TBAX halides were also tested with each of macrocyles **7**, **7a**, **10,** and **10a**, again, in analogous experiments to those conducted with the isophthaloyl macrocyclic amides[7] described above. In these tests, in $CDCl_3$ solutions, no ^{1}H NMR CIS were observed with **10** or **10a**.



Scheme 3. Synthetic routes to macrocyclic CTA-based bis- and tetra-sulfonamides.

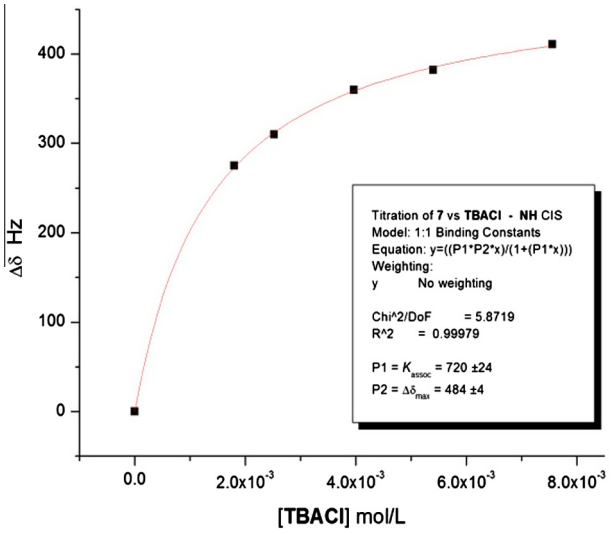


Figure 1. 1:1 Binding plots for the titration of **7** (0.62×10^{-3} M in $CDCl_3$) with TBACl using ^{1}H NMR (300 MHz) CIS for the N–H protons).

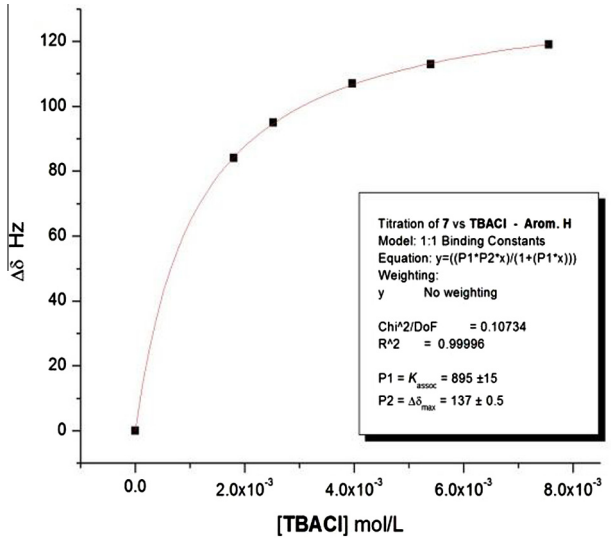


Figure 2. 1:1 Binding plots for the titration of **7** (0.62×10^{-3} M in $CDCl_3$) with TBACl using ^{1}H NMR (300 MHz) CIS for the intra-annular naphthyl protons.

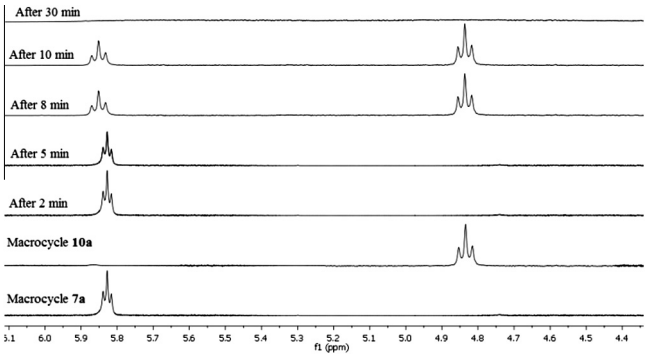


Figure 3. Expanded sections of ^{1}H NMR (300 MHz) spectra of the NH signals of **7a** and **10a** from the stepwise timed photo-chemical reaction of **7a**.

However, with **7** and **7a**, significant complexation could be determined: For **7** average K_{assoc} values of $808 \pm 18\ M^{-1}$; $229 \pm 16\ M^{-1}$, and $222 \pm 21\ M^{-1}$, respectively, and for **7a** average K_{assoc} values of $252 \pm 8\ M^{-1}$; $87 \pm 6\ M^{-1}$, and $52 \pm 5\ M^{-1}$, respectively, were determined for the chloride, bromide, and iodo salts. These values were determined using non-linear 1:1 binding isotherms[11] for the NH and aromatic intra-annular proton singlet CIS changes (see Figs. 1 and 2) which were averaged. The results confirmed the stronger relative affinities for the chloride anion as seen previously also with the isophthaloyl macrocyclic amides. The other 'non-complexing' anions tested, namely the tetrafluoroborate and phosphorus hexafluoride salts showed negligible chemical shift changes for which association constants could not be determined.

The association constants for **7** and **7a** are nearly 3-, 2.5-, and 4-fold higher for the Cl^-, Br^- and I^- salts, respectively. There are several possible factors which could account for these differences. Firstly, the mode of complexation of the halide ion is presumed to be via hydrogen-bonding between the halide ions and the protons of the NH groups. As found by others in similar studies, the trend is: $Cl^- > Br^- > I^-$. Secondly, the tetrabutylammonium ion is non-coordinating so it is presumed that the ether oxygen atoms are not as significant in the case of the TBAX salts compared with the metal halides. Since presumably the distances between the NH groups in the two macrocycles are not different, a factor that could

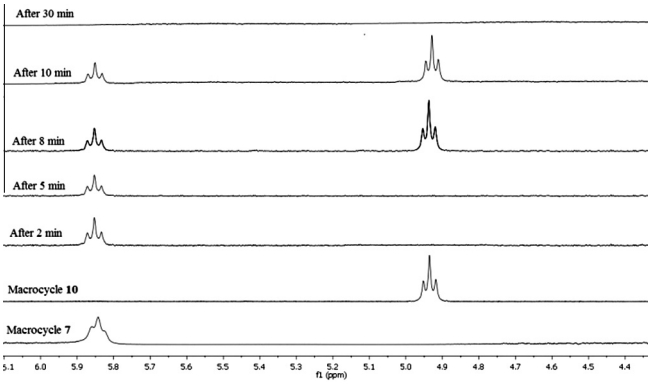


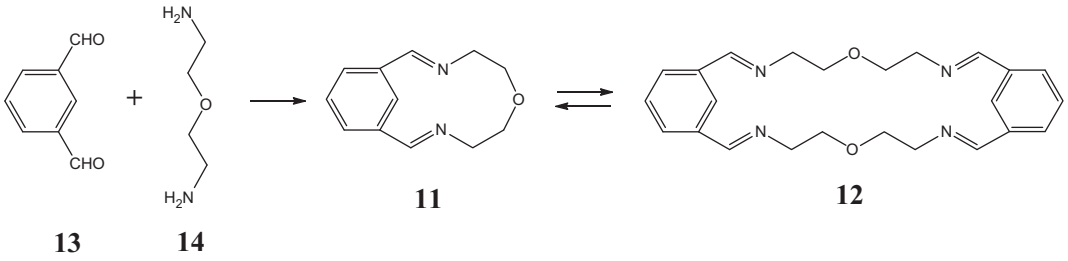
Figure 4. Expanded sections of ^{1}H NMR (300 MHz) spectra of the NH signals of **7** and **10** from the stepwise timed photo-chemical reaction of **7**.

be more significant is the difference in the ring sizes leading to more conformational possibilities and a larger entropic effect therefore which needs to be overcome in the case of **7a**.

ESI-mass spectral data were also determined qualitatively using ESI-mass spectra in both positive and negative modes and a summary table is given in the Supplementary data. In the negative-ion mode, for the TBACl:**7** solutions a *m*/*z* signal at 1515.8 corresponding to [**7**+Cl^-], and in the positive-ion mode, *m*/*z* signals at 1722 and 1781 corresponding to [**7**+TBA^+] and [**7**+TBACl+Na^+], respectively were present. For the TBABr:**7** solutions, in the negative-ion mode, signals at *m*/*z* 1561.8 corresponding to [**7**+Br^-], and in the positive-ion mode signals at *m*/*z* 1722 and 1803 corresponding to [**7**+TBA^+] and [**7**+TBABr+H^+], respectively were present. Using the same conditions and parameters for the ESI-MS spectra used in the previous cases for TBAI did not reveal signals in the positive-ion mode indicating any complexation. However, when the solvent was changed from chloroform to methanol, and the dry temperature was decreased on the chromatograph to 200 °C, the ESI-MS spectra in the negative-ion mode showed a *m*/*z* signal at 1607.9 corresponding to [**7**+I^-], and in the positive-ion mode, signals at *m*/*z* 1799 and 1849 corresponding to [**7**+TBA+$3H_2O$+Na^+] and [**7**+TBAI+H^+], respectively.

For **7a** the ESI-MS of the TBACl:**7a** solution in chloroform in the negative-ion mode showed a mass signal at *m*/*z* 1573 corresponding to [**7a**+Cl^-], and in the positive-ion mode mass signals at *m*/*z* 1779 and 1838 corresponding to [**7a**+TBA^+] and [**7a**+TBACl+Na^+], respectively. For the TBABr:**7a** solution the ESI-MS spectra in the negative-ion mode showed a mass signal at *m*/*z* 1617 corresponding to [**7a**+Br^-], and in the positive-ion mode, mass signals at *m*/*z* 1779 and 1882 corresponding to [**7a**+TBA^+] and [**7a**+TBABr+Na^+], respectively. But, as before, in the case of TBAI, using the same conditions and parameters of the ESI-MS spectra used for the chloride and bromide salts, no mass signals corresponding to any complexation in the positive-ion mode could be detected. However, when the solvent was changed from chloroform to methanol instead, and the dry temperature to 200 °C on the instrument, as was done with **7**, the ESI-MS spectra in the negative-ion mode did reveal a signal at *m*/*z* = 1663.6 corresponding to [**7a**+I^-] and in the positive-ion mode, signals at *m*/*z* 1779, 1798, and 1929 corresponding to [**7a**+TBA^+], [**7a**+TBA^++H_2O], and [**7a**+TBAI+Na^+], respectively.

All attempts to form suitable crystals for single-crystal X-ray analysis of each of the four products obtained, or from the complexation studies as their complexes, failed with the exception of **10a** itself which crystallized by the slow evaporation at room temperature of an aqueous methanol/ethyl acetate solution (see photochemistry section below however!). **10a** crystallized in the non-centrosymmetric orthorhombic space group $P2_12_12_1$, with intermolecular hydrogen bonding, leading to the formation of a



Scheme 4. Synthesis and equilibrium process of macrocycles **11** and **12** reported by Jurczak and co-workers.[18]

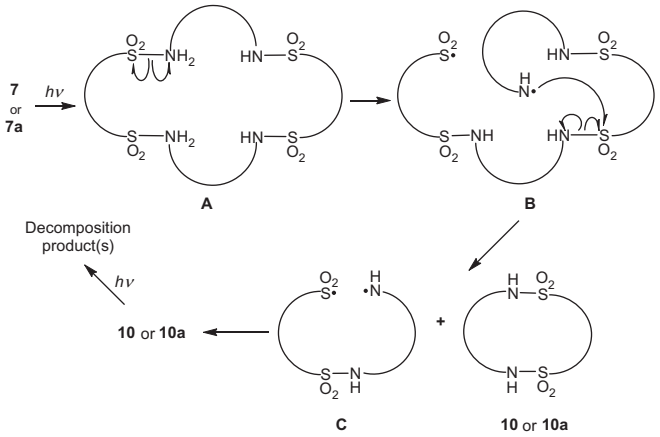
two-dimensional infinite polymer in the *ab*-plane (Figures S1–3 and Supplementary Table S1. Crystallographic data for **10a** (CCDC 924367) has been deposited with the Cambridge Crystallographic Data Centre).

When a chloroform solution of the [2+2] macrocyclic sulfonamide **7a** was set aside to crystallize from various solvents or solvent mixtures for three to four weeks in a closed vial on the benchtop, it was noticed that the color of the solutions gradually changed from colorless to light yellow. It was suspected that a photochemical reaction might have occurred, as similar solutions of the same compound which were protected from ambient light with aluminum foil did not change in the same way. By way of contrast, solutions of the [1+1] macrocyclic sulfonamide **10a** did not change in the same way, and afforded crystals whose X-ray structure was described above. When crystals did form from the methanol: chloroform solution of **7a**, it was anticipated that these would complement the X-ray structure for **10a**. Surprisingly, the X-ray structure of the putative **7a** however turned out to be identical to that obtained with **10a** itself. This observation indicated that a photochemical transformation of the [2+2] macrocycle formed the corresponding [1+1] macrocycle.

To confirm this hypothesis, a sample of **7a** was prepared by dissolving a small amount in deuterated chloroform in an NMR tube and then exposing the sample to a single low-energy 350-nm lamp in a photochemical reactor, for short periods and monitoring the solution directly by ^{1}H NMR. Preliminary experiments led to the optimal conditions which are summarized below. As can be seen in Fig. 3 increasing the light exposure time resulted in a gradual increase in the formation of the [1+1] macrocycle **10a**. This can be followed by comparing the triplet NH signals of the different spectra with the triplet NH signals of the reference macrocycles **7a** and **10a**. Thus, the [2+2] macrocycle can be seen to undergo a gradual conversion into the corresponding [1+1] macrocycle.

Additional support for this process was obtained from TLC monitoring and from the positive-mode APCI-mass spectra of the solution which had been irradiated for only 8 min which, in the positive mode, showed *m*/*z* signals at 769 and 1538 corresponding to the masses of [**10a**+H$^+$] and [**7a**+H$^+$], respectively. Sulfonamide **7** showed a similar photochemical behavior and was monitored by the ^{1}H NMR spectra from a similar timed 350-nm irradiation experiment (Fig. 4).

Photochemical reactions of sulfonamides in general have precedents in the literature and many are particularly of interest due to the fact that pharmaceutical aryl sulfonamide and sultam compounds may be photolabile.[12–14] Döpp, for example, conducted photochemical studies on sultams related to saccharin and proposed several mechanisms to account for the resulting photoproducts obtained.[15] In 1980 Lancaster and Smith reported the photochemical extrusion of SO_2 from 1,3-dihyrobenz[c]-2,1-isothiazoles to form a bicyclic benzazetine.[16] Weiss et al. also conducted a series of photochemical reactions on sulfonamides and included a photo-Fries rearrangement among several different pathways proposed to account for their observed products.[17]



Scheme 5. A proposed mechanism for the photochemical reactions.

The mechanism of the photochemical transformations which we observed in our examples can only be speculated upon. An analogous but non-photochemical disproportionation equilibrium process however was reported recently by Jurczak and co-workers[18] involving the macrocyclic [1+1] bis- and [2+2] tetra-imines **11** and **12** formed, respectively, by the condensation of dialdehyde **13** with the diamine **14** (Scheme 4).

In our instances however and under the condition studied, there was no evidence of an equilibrium process occurring, and a possible rationale for the observed transformation(s) which occur can be visualized in Scheme 5. It is presumed that a first step involves the hemolytic cleavage of a sulfur-nitrogen bond in **7** (or **7a**) as shown in **A** to form the diradical species **B** which can then undergo an intramolecular homolytic bond cleavage and concomitant formation of **10** from **7** (or **10a** from **7a**) and the diradical species **C** which can either form **10** (or **10a** from **7a**) or directly undergo formation of decomposition products.

In conclusion, two new bis-sulfonamide macrocycles **10** and **10a** and two *tetra*-sulfonamide macrocycles **7** and **7a** have been synthesized by reacting the ditosyl-protected CTA disulfonyl dichloride derivative 8 with the diamines **9** and **9a,** respectively, and a single-crystal X-ray crystal structure was determined for **10a**. Complexation studies of **7** and **7a** were conducted with both Group 1 and 2 chlorides and TBA salts using both ^{1}H NMR and ESI MS indicating that these new macrocycles were moderately good hosts for 1:1 complexation with TBAX halides. Finally, the [2+2] macrocycles **7** and **7a** were shown to be photolabile and unexpectedly formed the corresponding [1+1] macrocyclic compounds **10** and **10a**, respectively.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.081.

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