PAPER

( ) Check for updates

The synthesis of some novel stilbene dimers incorporating diamide tethers: studies in single electron transfer oxidation (FeCl₃)†

Maryam Sadat Alehashem, [iD] *[a] Azhar Ariffin,*[a] Amjad Ayad Qatran Al-Khdhairawi[b] and Noel F. Thomas*[a]

The FeCl₃ oxidative cascade reaction of the acetamido stilbene **1** which we reported some years ago produced the first atropodiastereomeric indolostilbene hybrid **3**. By contrast, recent investigation of the oxidation of the stilbene succinamide dimer **72** (FeCl₃/CH₂Cl₂) appears, on the basis of spectroscopic evidence, to have produced the bridged macrocyclic indoline **73**.

1. Introduction

Some years ago we discovered that the 3,5-dimethoxy substituted acetamido stilbene, **1** when exposed to FeCl₃ in CH₂Cl₂ proceeded in a mechanistically complex reaction to yield four products,[1] one of which was, unprecedented.

This atropodiastereoselective transformation gave rise to a product **3** incorporating a stilbene, an indole, a chlorodimethoxyphenyl substituent, two stereogenic axes and an intramolecular hydrogen bond resulting in a 14-membered pseudomacrocycle in the conformation shown, **3** (Scheme 1). This development raises the question of the effect of methoxy substitution since completely different products are obtained when the substitution pattern was changed from 3,5 to 3,4-dimethoxy.[2] The above transformation raises the intriguing possibility that a macrocyclic variant of this reaction may be a realistic possibility. To the best of our knowledge, macrocyclic synthesis *via* oxidatively generated tethered amino stilbene radical cations, has not previously been reported. To put this development into a wider context, Boger reported a powerful and versatile Pd(0) mediated indole macrocyclisation that resulted in the synthesis of chloropentin/DEF molecules[3] (Scheme 2).

The Boger group noted that free radical and peptide coupling strategies failed[3] to deliver the macrocycles **5** and **6**. For other examples of palladium mediated heterocyclic/macrocyclic construction see the work of Harrowven,[4] Ohno,[5] Martin[6] and Parker.[7]

Some years earlier in a fascinating exploration of the radical-mediated transannular/Diels Alder reaction, Jones[8] reported that treatment of **7** with tributyltin hydride/AIBN gave rise to the tricycle **11** *via* 13-endo dig and Diels Alder reactions (Scheme 3).

By contrast, when Pattenden *et al.* treated the iodopropyl furan derivative **12** with tributyltin hydride, the intermediate formed by 12-endo dig ring closure underwent furan cleavage **14** followed by 5-exo trig ring closure **15** to yield the tetracyclic ketone **16**, Scheme 4.

The Pattenden syntheses above generated macrocyclic intermediates which are an efficient means to the desired ends that is, the macrocycles are not the final products. By contrast in the next few examples, the macrocycles are the intended targets. For example in the synthesis by Endo, the macrocyclic final products incorporate diamide tethers. Endo,[9] linked two molecules of L-cysteine **19** by means of adipoyl chloride **18**. The corresponding diester diamide was exposed O₂ in Et₃N/DMF at 25 °C to yield the bisdisulphide macrocycle, **21** (Scheme 5).

The concept of the tethered stilbene has been illustrated by the work of Mizuno.[10] Parabromobenzaldehyde **22** was exposed to TiCl₄/Zn to yield the paradibromo stilbene **23** by McMurry coupling. Treatment of **23** with *t*-BuLi gave the dilithiated species (**24**) which then reacted with 1,3-bis[[(chlorodimethylsilyl)methyl]benzene **25** to produce the *trans,trans* stilbenophane **26**. Photoreaction of **26** gave rise to the tethered cyclobutane macrocycles[10] **27** and **28**. Again to the best of our knowledge, no stilbene dimers incorporating diamide ethers based on succinamide or adipoylamide have been reported and studied from the point of view of FeCl₃ promoted cyclisations. This brings us to the next section where this novel concept is described (our synthetic plan).

2. The synthetic plan

The Mizuno study we have just described (Scheme 6) established the principle that two stilbenes could be held together by

[a]Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia. E-mail: maryam.alehashem@yahoo.com; azhar70@um.edu.my; noelfthomas@um.edu.my; noelfthomas@yahoo.com
[b]Atta-ur-Rahman Institute for Natural Product Discovery, Faculty of Pharmacy, Universiti Teknologi MARA Selangor Branch, 42300 Puncak Alam, Selangor, Malaysia
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra12534h
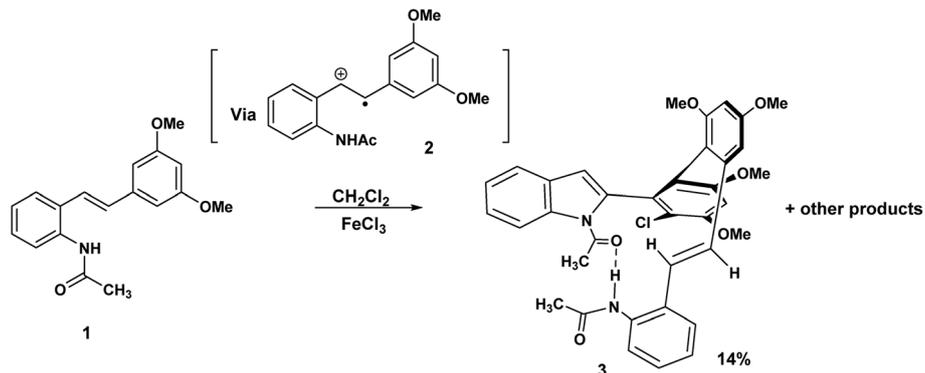
Scheme 1   A radical cation mediated synthesis of an indolo stilbene hybrid.
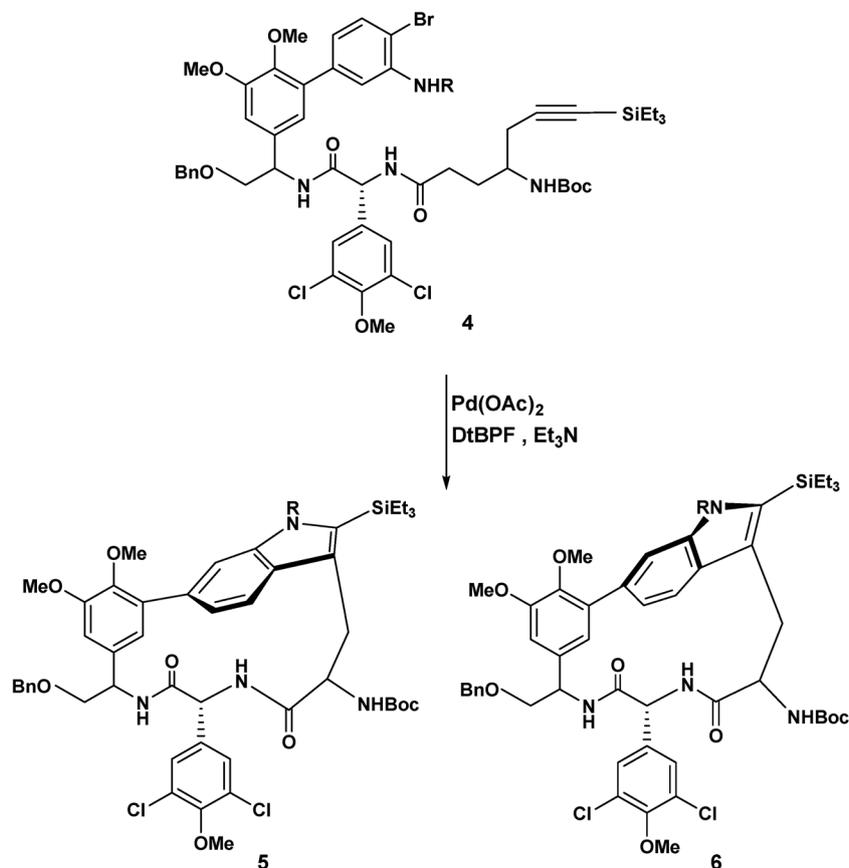
Scheme 2   Boger's application of the Larock annulation to macrocyclic construction.

a silane tether in preparation for cycloaddition. Our confidence in viability of our diamide tethered Heck precursor strategy was further encouraged by the report of Parker[11] in which the bicyclo-[4.2.0]-octadiene **29** was prepared in racemic form in seven steps. Treatment of **29** with adipoyl chloride, DMAP, CH_2Cl_2, gave the two adipoylamide octadiene dimers; a racemic modification and the C-2 symmetric compound **31**. By way of illustration, when the racemic compound was exposed to the antimony hexachloride complex (a cation radical salt), a penta-cyclic bislactone macrocycle **34** was obtained. This bis lactone was eventually transformed to the natural product (+)-Kingianin

(A).[11] The literature reveals many elegant applications of the cation radical Diels Aleder reaction[12–17] (Scheme 7).

We believed we could adopt diacid chlorides like **30** to prepare our novel dimers as described below. Our basic plan is shown in Scheme 8.

3.   Results and discussion

Although the iodophenyl malonamide dimer **37** could be prepared in moderate yields (Scheme 9), for reasons we will revisit later, the attempted double Heck coupling proved to be
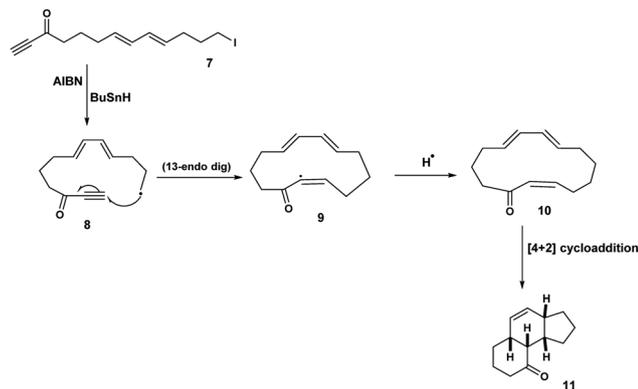
Scheme 3 Macrocyclic precursors *en route* Diels Alder reaction.
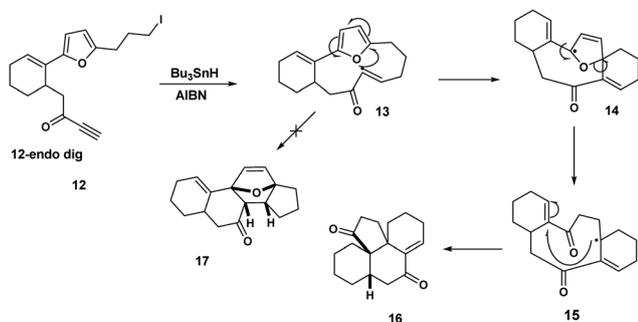
Scheme 4 Pattenden's radical mediated synthesis of a tetracyclic ketone *via* macrocyclic precursors.
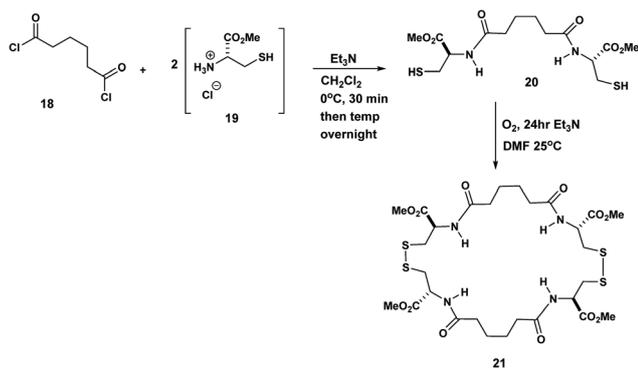
Scheme 5 Exploitation of adipoyl tethered cysteines in macrocyclic disulphide synthesis.

disappointing. We surmised that the coupling of the palladium reagent to the two amide carbonyls to give a six membered chelate inhibited the oxidative insertion step in the Heck reaction. To the extent that the presence of two NH'S contributes to this problem, protection of both amide nitrogen by the SEM protecting group in addition to changing both the palladium reagent and the inclusion of a ligand would improve the efficiency of the Heck coupling probably by promotion of the all important oxidative insertion into the aryl indole bond. An alternative reagent combination[18] $Pd_2(dba)_3/Pd(t\text{-}Bu_3P)_2$ could

have been tried. These alternatives notwithstanding, we opted for a revised strategy. In this approach the amino stilbene monomer was constructed by the Heck procedure followed by a double acylation with the appropriate diacid chloride. This revised procedure is depicted below.

The optimum conditions for the Heck, in contrast to our previous experience with various ortho amido stilbenes,[19] was to dissolve the iodoaniline **35** in dry CH_3CN under nitrogen with heating to 80 °C. Palladium acetate, Et_3N and 2-furyl phosphine[20] were then added in this order followed by 3,4-dimethoxystyrene **40**. Refluxing continued until the starting material was consumed. Similar conditions were exploited by Heck in the course of a synthesis of a more functionalized version of our amino stilbene.

The double acylation reaction proved to be much more challenging. In our early attempts malonyl chloride was added dropwise to a solution of the amino stilbene in dry CH_2Cl_2. This led to a complex mixture from which, after chromatography, only 22% of the desired product could be isolated. The complications associated with preparing amides by the acid chloride procedure are by now well known as the extensive the peptide and related literature clearly indicate. Ketene formation and associated side reactions are to be expected. Although many ingenious methods for tacking these problems by activation of the corresponding carboxylic acids, have been developed, we found that when the amino stilbene was added slowly dropwise to malonyl chloride for 1 h at 0 °C, we obtained the best yield of the corresponding dimer (65%). By means of this improved procedure the corresponding dimers incorporating succinyl ($n = 2$), glutaryl ($n = 3$) and adipoyl amides ($n = 4$) tethers were prepared in comparable yields.

Mechanistic hypotheses/predictions dependent on radical cation reactive conformations

In Scheme 8, we indicated that **38** when exposed to $FeCl_3$ would be expected to undergo polycyclisation/macrocyclisation. The text "carbon-centred free radicals and radical cations" edited by Forbes[21] in worthy of careful study. We have described the chemistry of radical cations in a review entitled: the radical cation mediated cleavage of catharanthine leading to the vinblastine type alkaloids: implications for total synthesis and drug design.[22] Radical cation/intact olefin and diradical cation pathways (assuming oxidation of both olefinic bonds) need to be considered (Scheme 10).

In the first proposed pathway, the stilbene **43** has undergone single electron transfer oxidation of one of the olefinic bonds to yield the monoradical cation **44**. Intramolecular nucleophilic attack by the NH **44** will give rise to the indolyl radical **46** which subsequently attacks the intact olefin at the C-7‴ position to yield the C-7″ macrocyclic radical **47** which undergoes oxidation to the corresponding benzylic carbocation and a second intramolecular capture should result in the bisindoline **49**, Scheme 11.

Our speculation regarding diverse pathways for our tethered stilbene radical cation continues in Scheme 12. The key intermediate in this case the diradical cation **50** resulting from
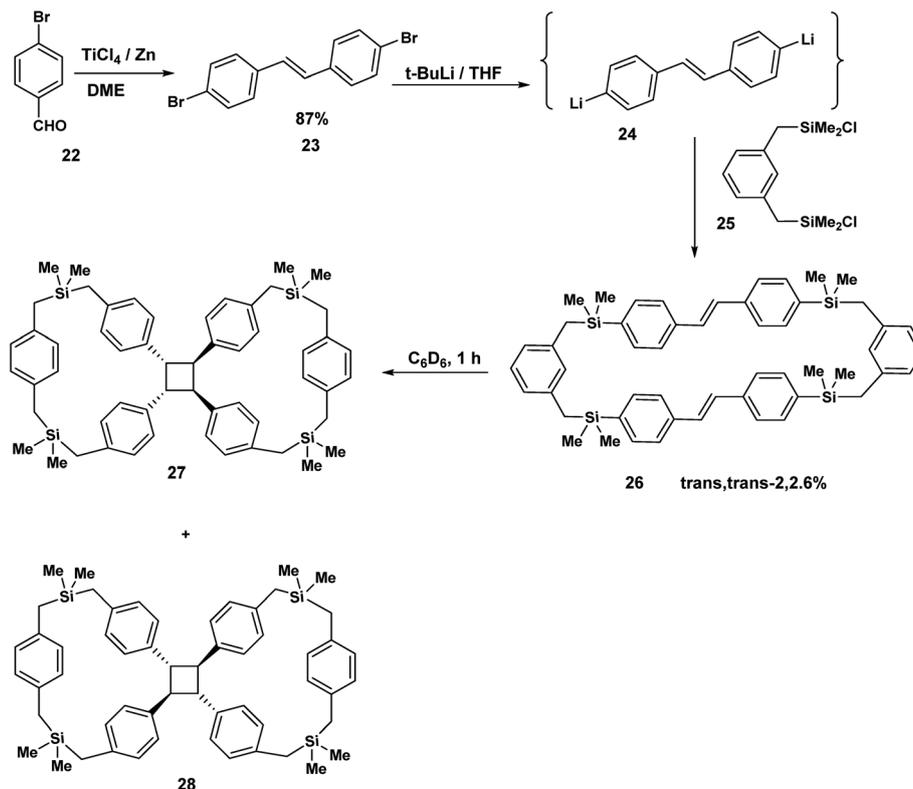
Scheme 6 Stilbenophanes (generated by the McMurry reaction) transannular precursors of the cyclobutane macrocycles.

oxidation of both olefinic bonds. In intermolecular variants of amino stilbene (or amido stilbene) oxidative dimerisation under electrochemical conditions, a high concentration of the stilbene radical cation is believed to be present on the electrode surface.[23,24] Under conditions of ferric chloride oxidation, radical cation intact olefin dimerisations would appear to be reasonable given the presumption that the radical cation is in a low concentration although this is not a hard and fast rule. In any event we are in this report dealing with tethered stilbenes and therefore it would prudent to keep an open mind. With the

formation of the diradical cation **50** (Scheme 12) radical combination (assumed to precede cyclisation) would give rise to the dication species **51**. Double intramolecular capture of the dication will yield either the mesobisindoline **52** from the erythro intermediate **51** or alternatively, the racemic bisindoline **55** *via* the threo dicationic intermediate **54** (Scheme 12).

Continuing our mechanistic speculation, we see in Scheme 13 the intramolecular example of crossover nucleophilic capture, the intermolecular variant of which we have described previously.[25] The tethered dication must adopt a reactive
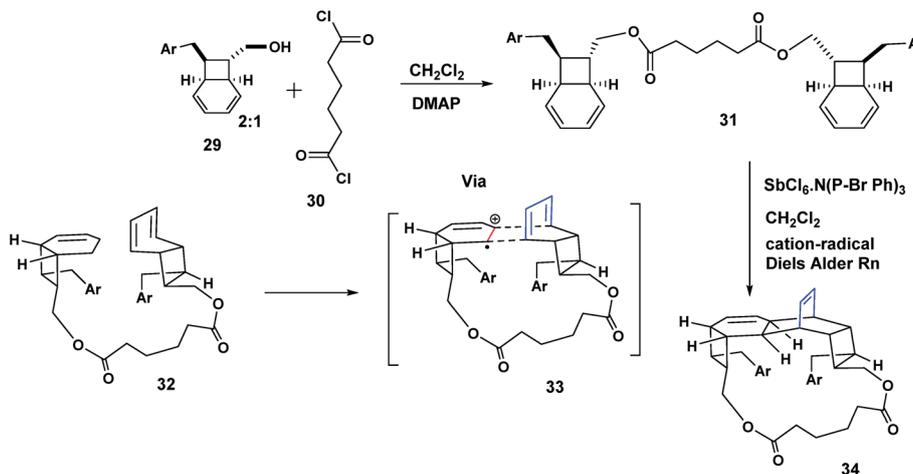
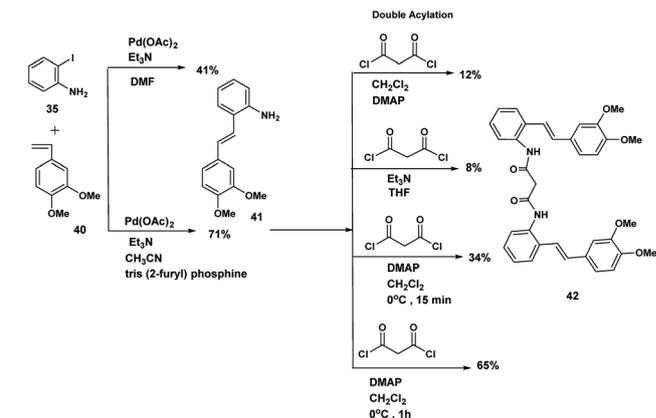**Scheme 7** Parker's use of an adipoyl tether for an intramolecular cation radical Diels Alder reaction.
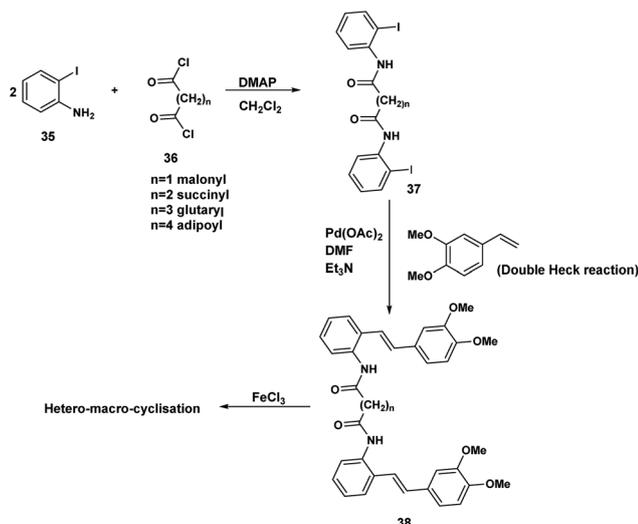
Scheme 8 Our synthetic plan for the preparation of diamide tethered stilbenes.

Scheme 10 Heck coupling/double acylation.

conformation that prohibits direct nucleophilic capture on the benzylic carbenium ions **56** of the type described in Scheme 12. The "macrocyclic" bisisoquinolines with cis ring fusion **57** would be the result (Scheme 14).

In Scheme 14, we see another example of radical cation intact olefin dimerisation. Intramolecular attack by the radical **58** on the intact olefin results in a second benzylic radical [**59** to **60**] after intramolecular capture of the benzylic carbocation **59** (Scheme 14). Further oxidation and deprotonation would proceed to yield the indolostilbene hybrid **61**. Any strain inherent in such a structure would be alleviated for higher values of *n* (*e.g.* 3, 4 *etc.*). A different reactive conformation is depicted in Scheme 15 [compare **62** (Scheme 15) with **58** (Scheme 14)]. In this alternative the radical cation, through the of the C-7′ radical, attacks the intact olefin. This sets up the a biaryl link as a result of delocalisation C(7″) radical (not shown) (Scheme 15). Oxidation and deprotonation gives rise to the bridged fused 8 : 10 ring system incorporating an indoline moiety **65**.

The cascade sequence depicted Scheme 16 is in contrast to Scheme 15. In the earlier scheme the C(7′) radical **62** underwent

delocalisation and subsequently biaryl coupling **63**. By contrast (Scheme 16), the C(7″) radical undergoes rapid oxidation [**67** to **68**] to yield the carbocationic intermediate **68** which undergoes intramolecular electrophilic aromatic substitution **68** and rearomatisation leading to **70**.

## Preliminary reflections on the FeCl$_3$ promoted cascade reactions

When the aminostilbene succinamide **72** was exposed to FeCl$_3$ (in a 1 : 1 molar ratio) in CH$_2$Cl$_2$, **73** was obtained as the major product. A comparison of the NMR spectroscopic features of starting material and this product is intriguing.

In examining the aromatic region of 400 MHz NMR spectrum of the proposed structure **73** (Scheme 17) we note that the overlapping pair of doublets, integrating for three protons, at 6.48 ppm correlate with triplets at 7.18 and 7.3 ppm according to the COSY spectrum. The *J* value of 10.32 Hz is consistent with the ortho coupled C(3‴) C(4‴) and C(6‴) and C(5‴) protons of the A′ ring. The *J* value of 10.3 Hz is slightly outside the normal range for such protons it is interesting to note that the C(6‴) and C(3‴) protons of the A′ **73** have experienced much greater shielding compared to the starting succinamide **72** and the corresponding protons of the A ring of the dimer. This is because the C(6‴) proton experiences a repulsive interaction
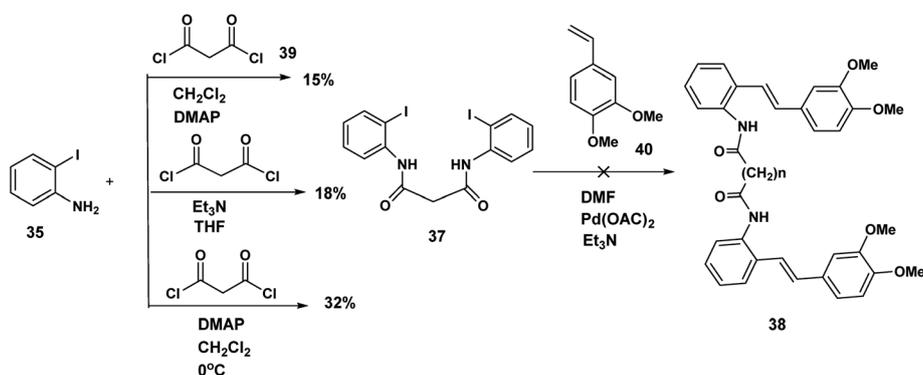

Scheme 9 Attempted double acylation/double Heck.
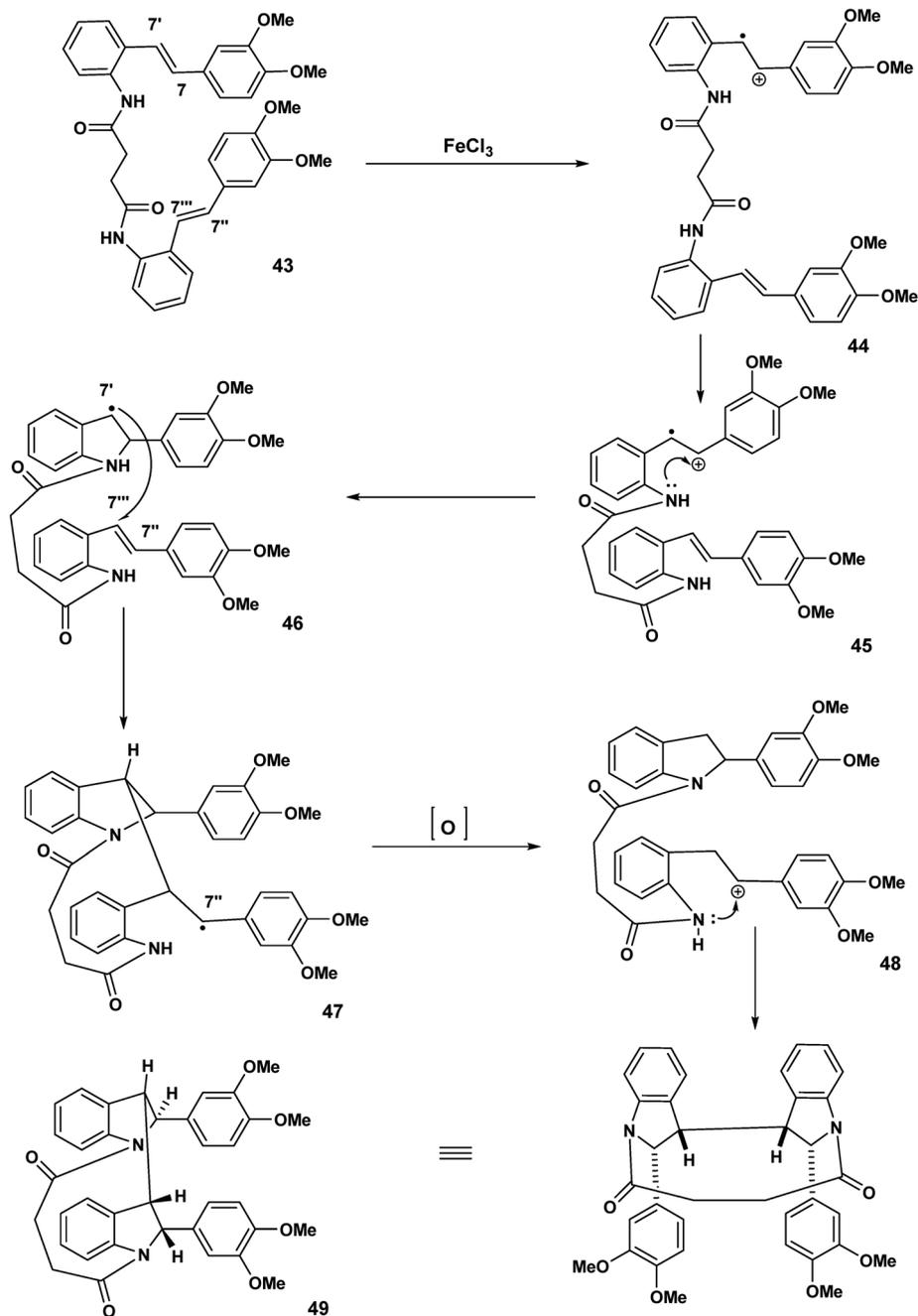
Scheme 11 Intramolecular attack of a radical cation on an intact olefin.

with the $C(7''')$ methine proton (as the physical model reveals) and the $C(3''')$ proton is in close proximity to the methylene protons of the succinamide tether (Fig. 1). On the other hand the physical model indicates a more congested environment for this A′ ring system compared with the A ring system (and compared to the starting stilbene succinamide dimer **72**) which accounts for the unusual shielding of the $C(6''')$ and $C(5''')$ protons. In the case of the latter, we observe a second set of doublets at 6.85 and 6.9δ which also correlate with the set of triplets in the region 7.27 to 7.4δ. These peaks are more deshielded with coupling constants of 7.24 and 7.28 Hz (more

normal values). This is consistent with a less crowded environment for the A ring system. Overall these correspond to the doublet–triplet–triplet–doublet pattern represented by the A and A′ ortho substituted aniline ring systems. We believe that the correlating doublets at 6.45 and 6.75 ppm correspond to the protons on the B′ ring system *i.e.* $C(5')$ H and $C(6')$ H (a classic AB pattern). It is worth noting that there are three broad aromatic singlets at 6.78 and 6.94 ppm with one more hidden under the broad doublet at 6.5 ppm which integrates for 3 protons. By of comparison, the starting stilbene succinamide dimer **72** has a doublet at 6.87 ppm corresponding to $C(2)$–H. By
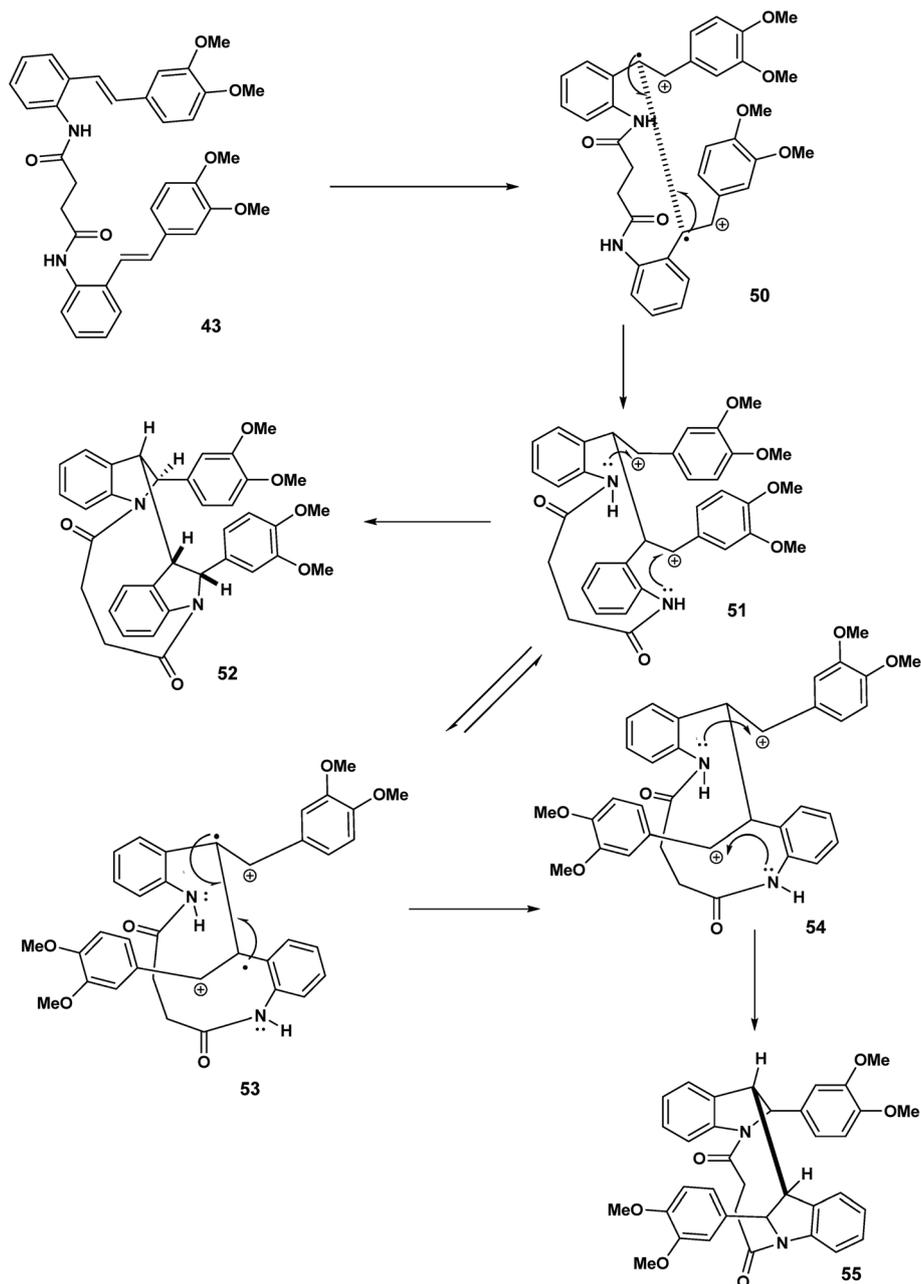
Scheme 12 Formation of meso and racemic bisindolines *via* **51** and threo **54** dicationic intermediates.

contrast for the product **73** there are two broad singlets (at 6.94 and 6.78 ppm) with the third singlet we believe to be hidden under the broad doublet at 6.48 ppm. These singlets correspond to C(2)–H, C(5)–H and C(2′)–H. We now examine the aliphatic region of the spectrum. The four methoxy singlets that cover the region 3.77 to 3.96 ppm indicate the disruption of symmetry in the product **73** compared to the starting material **72** (Scheme 17). It is noteworthy that in the ^{13}C spectrum of **73**, the four CH$_3$ (carbons) are clearly visible and partially overlapping at 55.05, 55.99, 55.86 and 55.93 ppm. From an examination of the HMQC and ^{13}C DEPT spectrum. This suggests a disruption of symmetry which is all the more evident the ^{13}C data is compared with that

of the starting aminostilbene malonamide **72** where the four methoxymethyl carbons overlap to a degree. It is interesting that we have two distinctive singlets at 4.2 and 3.4 ppm. We believe that these singlets correspond to the C(7‴)–H and C(7″)–H protons located at two of the four contiguous asymmetric centres. The virtually orthogonal relationship of the protons at C(7″)–H, C(7‴)–H and C(7′)–H accounts for the appearance of the C(7‴)–H and C(7″)–H protons as singlets. We would expect the C(7′)–H and C(7)–H protons to appear as doublets. We suspect that these protons are subsumed under the broad peak at 2.06 ppm. This broad peak partly masks a small impurity. These features are consistent with our proposed structure and
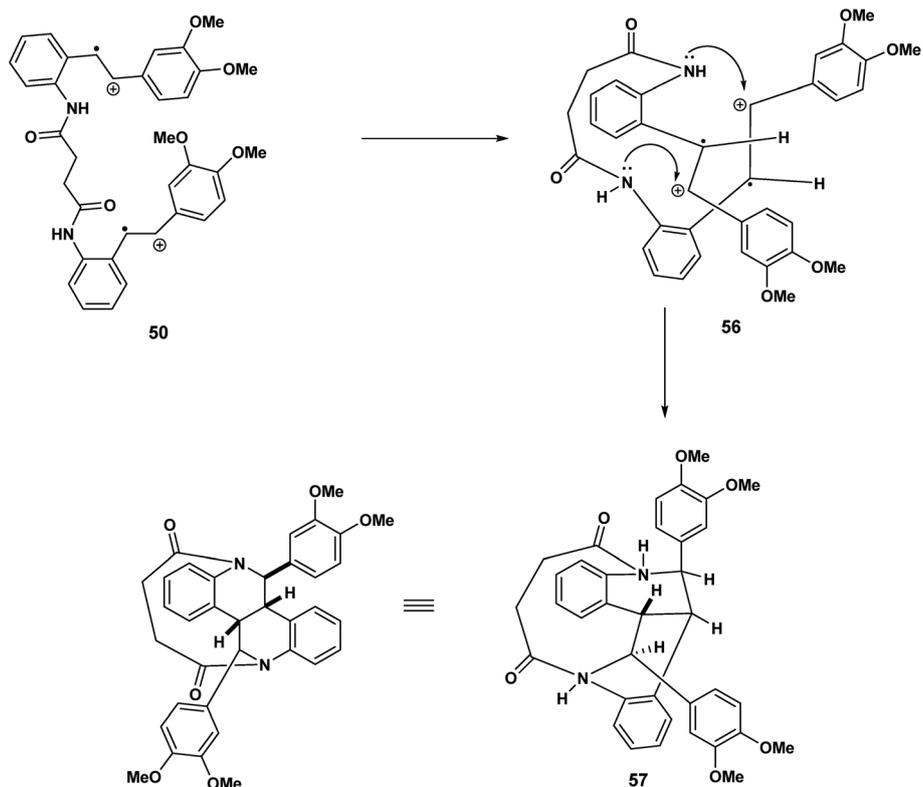
Scheme 13 Double intramolecular (cross over capture) of dicationic species **56**.
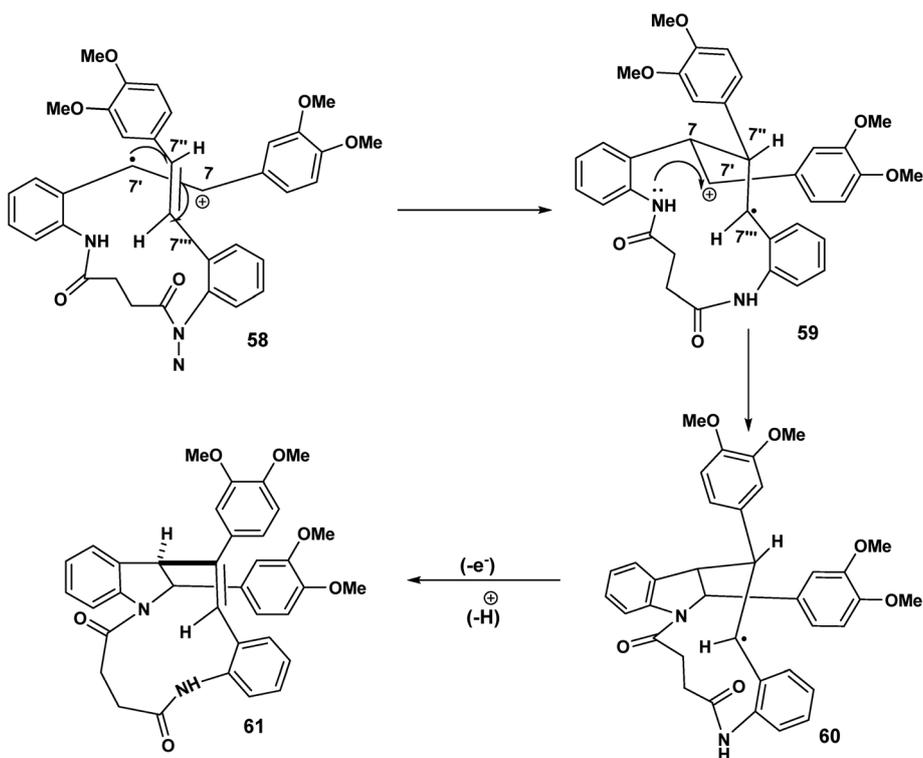
Scheme 14 12-endo trig (for *n* = 1) cyclisation of the C(7′) radical culminating in the indolostilbene **61**.
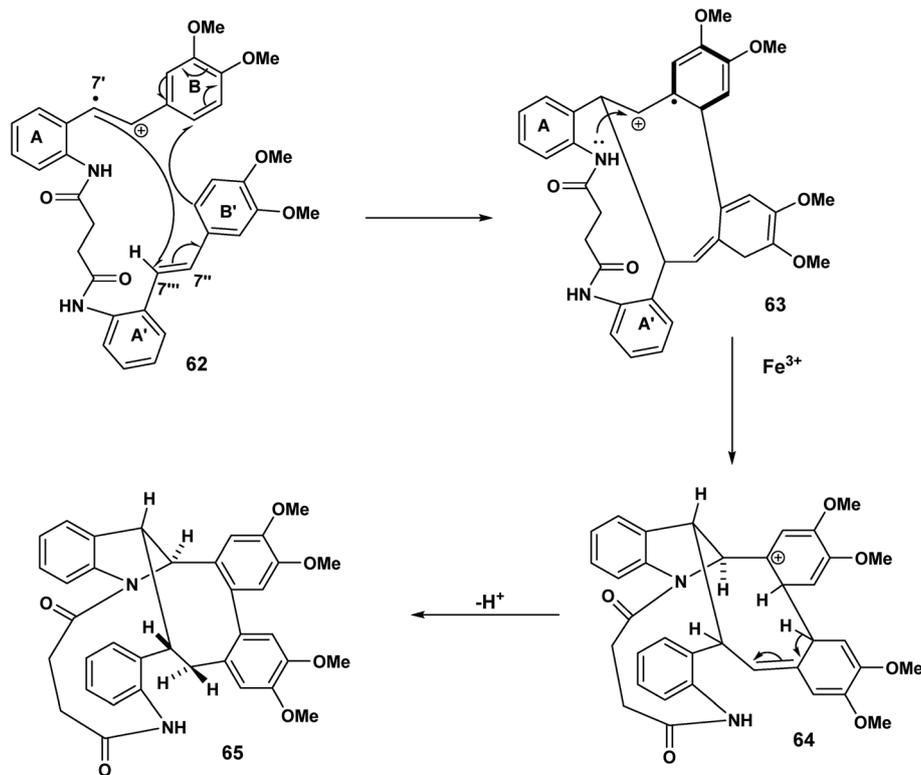
Scheme 15 11-endo trig for ($n = 1$) cyclisation of the C(7′) radical biaryl formation.

account for the at first surprising upfield shift of these protons. We now turn our attention to the ^{13}C spectrum with respect to the methine carbons corresponding to C(7‴) and C(7″). There carbons in the HMQC are found at 47 and 50 ppm respectively. These peaks relate to the proton spectrum where C(7″) is at 4.2 and C(7‴) at 3.4 ppm. C(7″) is clearly more deshielded because of the electron withdrawing effect of the B and B′ aromatic rings. The other two methine carbons can be found under the region 26 to 28 ppm and are thus related to the corresponding protons under the broad peak at 2.06 ppm (from the HMQC) (the carbon 13 peaks are admittedly weak and impurities in that region complicate matters but the HMQC places these methine carbons at about 27 ppm). It is significant that the C(7) and C(7′) methine protons are in more sterically congested environments due on the one hand, to the environment of the succinamide moiety and the A′ ring and on the other, the B′ ring in a pseudo 1,3-diaxial interaction with the C(7′) proton (there is of course another pseudo 1,3-diaxial interaction between the C(7) proton and the A′ ring). This explains the upfield shift of these methine protons in the proton spectrum. Notice that the broad peak we have mentioned at 2.06 ppm most likely includes the N–H which is more shielded compared to other systems we have studied. The succinyl protons that appeared as a sharp peak (singlet) integrating for four protons at 2.87 ppm in the starting stilbene succinamide dimer, now appear as a broad multiplet at 3.18 in **73**. The broad peak at 2.06 ppm integrates for three protons (the C(7), C(7′) and NH protons). These intriguing

features among others are a consequence of conformational effects inherent in the bridged macrocyclic super structure.

We ruled out a structure to **57** (Scheme 13) as this is clearly a symmetrical structure which would yield two distinctive methoxy singlets which would not fit the NMR data for our macrocycle. The structure **61** (Scheme 14) was also ruled out as apart from the methylenes of the succinyl moiety, only two aliphatic CH signals would be expected (methoxy signals excluded). A physical model demonstrated that **65** (Scheme 15) would be two highly strained and this was subsequently ruled out. Notice that alternative structures **52** and **55** (Scheme 12) can also be excluded as either of these should give rise to only two methoxy signals in the NMR spectrum (Fig. 2 and 3).

4. Conclusion

Although the evidence presented is not, at this stage incontrovertible, we believe the proposed structure **73** is the best fit for the spectroscopic evidence and the evidence of the physical model. Therefore in the circumstances in which we find ourselves, we are compelled to present these significant results which suggest that we have here the first example of a macrocyclic bridged indoline generated by exposure of a hitherto unknown bis amino stilbene succinamide **72** to the single electron oxidant $FeCl_3$. We hope, in more favourable circumstances, to present the results of a more comprehensive investigation in the future.
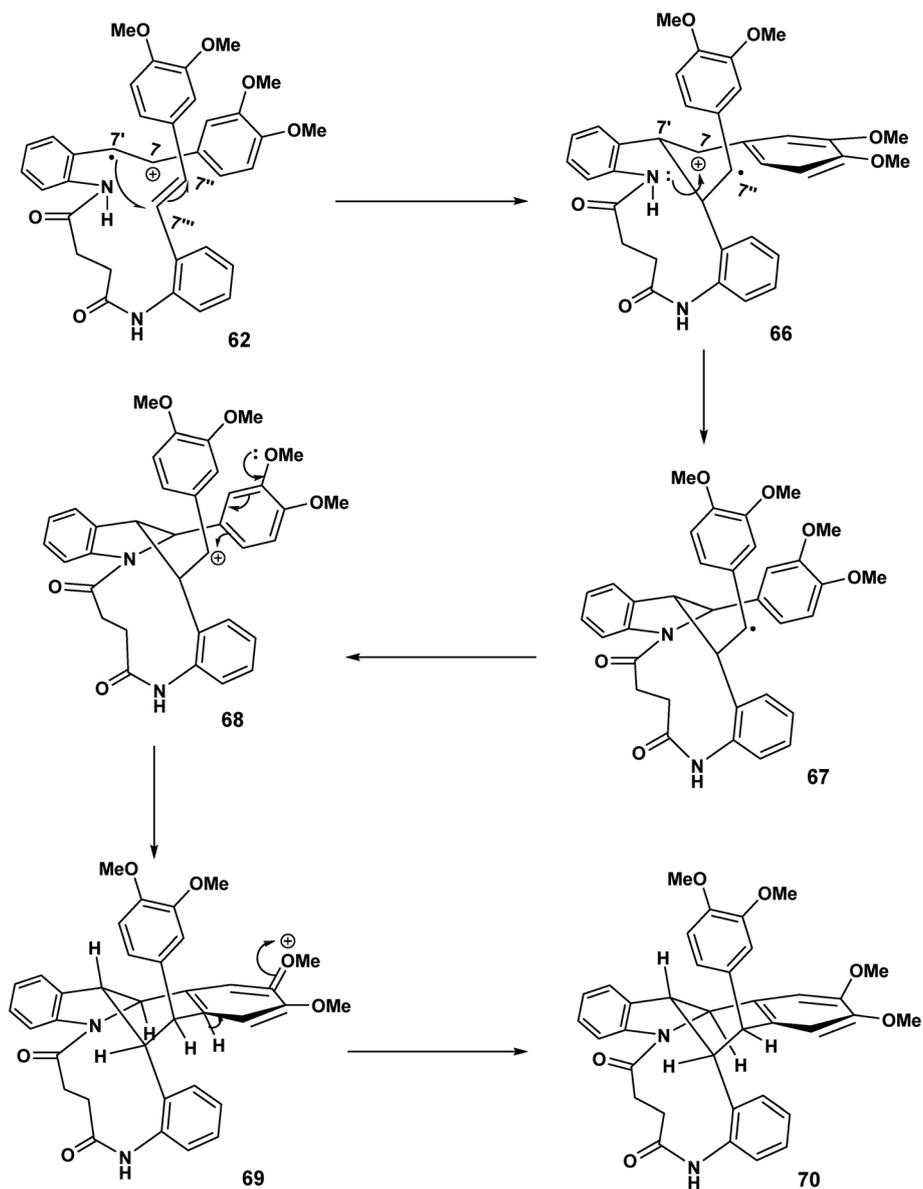
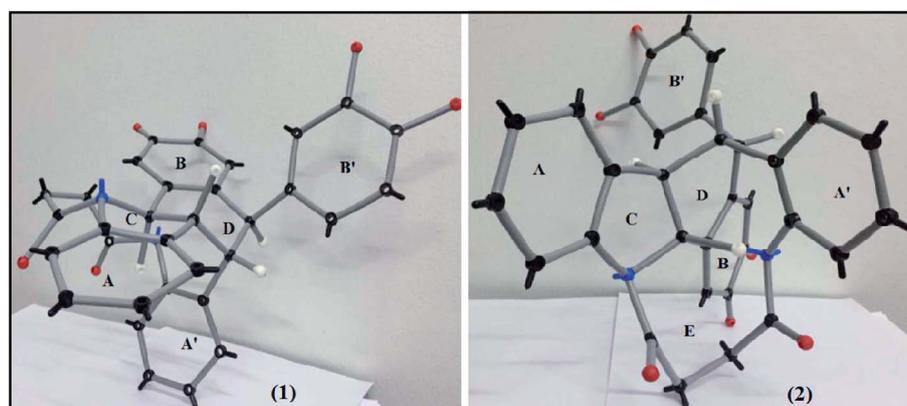Scheme 16   11-endo trig ($n = 1$) ring closer, oxidation, electrophilic aromatic substitution leading to 70.
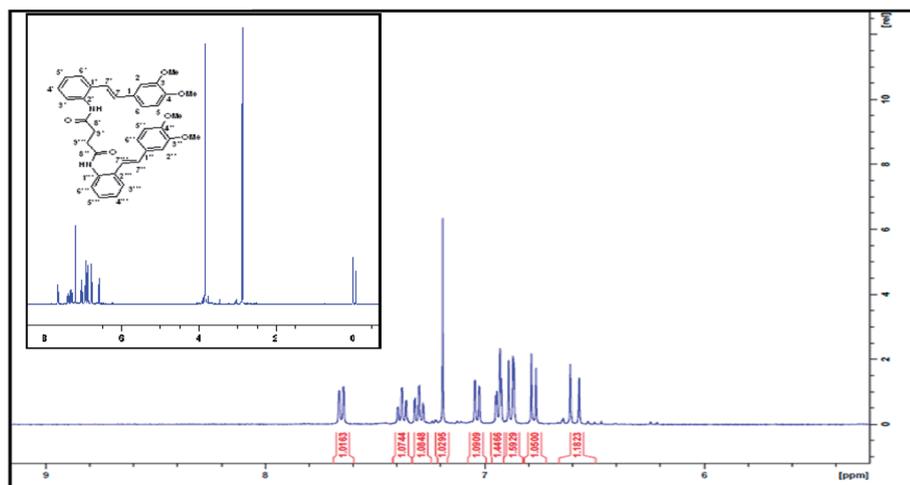

Fig. 1   Two views of the physical model of 73.

Fig. 2 ^{1}H NMR (CDCl$_3$, 400 MHz) spectrum of compound bis(2((*E*)-(3,4-dimethoxystyryl)phenyl)succinamide).
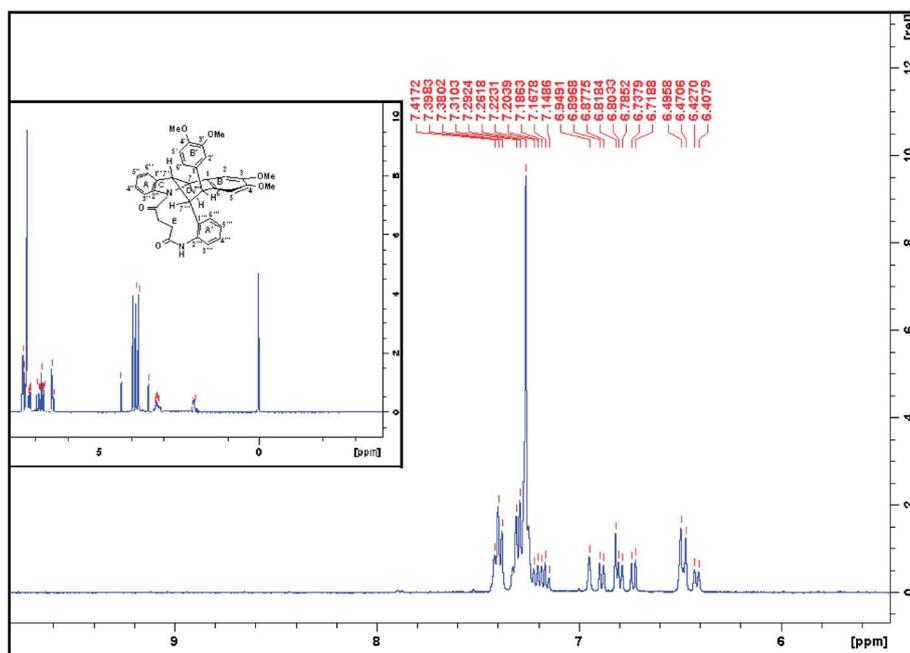

Fig. 3 ^{1}H NMR (CDCl$_3$, 400 MHz) spectrum of compound (**73**) Scheme 17.

5. Experimental

General remarks

Unless otherwise noted, materials were purchased from commercial suppliers and used without purification. Column chromatography was performed using Merck silica gel (0.040–0.063). IR spectra were recorded on a perkinElmer spectrum 400 FTIR/FT-FIRspectrophotometer were used; for centrifugal chromatography, Merck silica gel 60 PF$_{254}$ containing gypsum were used. Nuclear magnetic resonance (NMR) spectra were obtained on a JEOL FT-NMR BRUKER AVN 400 and JEOL FT-NMR LA400 spectra are reported in units of ppm on the scale, relative to chloroform and the coupling constants are given

in Hz. Mass spectra were measured using Agilent 6530 Accurate Mass Q-TOFLC/MS system.

Phase I: preparation of (*E*)-2-(3,4-dimethoxystyryl)aniline (71) (see Table 1)

In a dry, two necked flask, the desired 2-iodo aniline (1 g, 4.56×10^{-3} mol) was dissolved in dry CH$_3$CN (8 ml) and stirred under nitrogen. The solution was heated at 80 °C and refluxed for a few minutes. Palladium(II) acetate (0.0102 g, 4.56×10^{-5} mol) was added, followed by triethylamine (2.5 ml, 4.56×10^{-3} mol) and 2-furyl phosphine (0.042 g, 1.82×10^{-4} mol). 3-4 Dimethoxystyrene (0.93 g, 5.9802×10^{-3}) was then added to the reaction flask. The reaction mixture was heated under
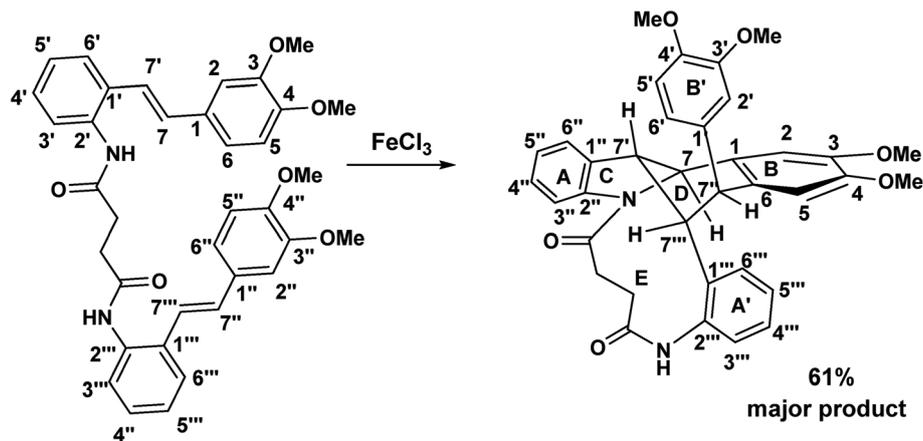
Scheme 17 A bridged macrocyclic indoline diamide.

reflux for 3 h and stirring continued overnight at room. When the TLC indicated the complete consumption of starting material, the mixture was extracted with ethyl acetate (3 × 30 ml) and washed distilled water (3 × 30 ml). The resulting organic extracts were combined and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (7 : 3 hexane : ethyl acetate) afforded the desired product (71% yield).

(E)-2-(3,4-Dimethoxystyryl)aniline. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.90 (3H, s), 3.93 (3H, s), 6.72, (1H, d, J = 7.8 Hz), 6.81 (1H, t, J = 7.8 Hz), 6.86 (2H, d, J = 8.2 Hz), 6.94 (1H, d, J = 16.0 Hz), 7.03 (1H, d, J = 16.0 Hz), 7.09 (1H, t, J = 7.8 Hz), 7.04 (2H, d, J = 8.2 Hz), and 7.38 (1H, d, J = 7.6 Hz); ^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz) δ 55.93, 55.98, 108.9, 111.04, 116.2, 117.73, 128.5, 127.29.5, 124.15, 127.2, 128.39, 130.21, 130.81, 143.81, 148.9.

Phase II: preparation of bis (2-(E)-(3,4-dimethoxystyryl)phenyl) malonamide (42) (see Table 1)

To a stirred solution of the malonyl chloride (0.027 g, 1.95 × 10^{-4} mol) prepared as above, and DMAP (0.052 g, 4.3 × 10^{-4} mol) in CH$_2$Cl$_2$ (4 ml), was added slowly dropwise amino stilbene (0.1 g, 3.9 × 10^{-4} mol) at 0 °C. The stirring was continued overnight and the reaction allowed warm to room temperature when TLC indicated complete consumption was extracted with ethyl acetate (2 × 30 ml) and the washed with distilled water (2 × 30 ml). The resulting organic extracts were combined and evaporated under reduced pressure to yield crude product. Purification by column chromatography (7 : 3 hexane : ethyl acetate) afforded the desired product (65% yield).

((E)-2-(3,4-Dimethoxystyryl)phenyl)malonamide. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm: 7.04 (s), 6.69 (d, J = 8.2 Hz), 6.93 (d, J = 8.2 Hz), 7.05 (d, J = 16 Hz), 7.52 (d, J = 7.8 Hz), 7.19 (t, J = 7.8 Hz), 7.23 (t, J = 7.8 Hz), 7.75 (d, J = 7.8 Hz), 6.84 (d, J = 16 Hz). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm: 133.7, 108.6, 140.0, 141.9, 120.57, 120.34, 130.02, 130.04, 124.21, 126.16, 127.7, 130.04, 131.12, 165.62, 44.83, 55.69, 55.87.

Phase III: preparation of bis(2((E)-(3,4-dimethoxystyryl) phenyl)succinamide) (72) (see Table 1)

To a stirred solution of the succinyl chloride (0.030 g, 1.95 × 10^{-4} mol) and DMAP (0.052 g, 4.3 × 10^{-4} mol) in CH$_2$Cl$_2$ (4 ml) was added amino stilbene (0.1 g, 3.9 × 10^{-4} mol) drop wise at 0 °C. The stirring was continued overnight and the reaction allowed to warm to room temperature. When the TLC indicated the complete consumption of starting material, the reaction mixture was extracted with ethyl acetate (2 × 30 ml) and the washed with distilled water (2 × 30 ml). The resulting organic extracts were combined and evaporated under reduced pressure to yield crude product. Purification by column chromatography (7 : 3 hexane : ethyl acetate) afforded the desired product (67% yield).

((E)-2-(3,4-Dimethoxystyryl)phenyl)succinamide. ^{1}H NMR (CDCl$_3$, 400 MHz) δ ppm 6.86 (s), 6.76 (d, J = 8.2 Hz), 6.92 (d, J = 8.2 Hz), 6.89 (d, J = 16 Hz), 7.02 (d, J = 7.8 Hz), 7.31 (t, J = 7.8 Hz), 7.28 (t, J = 7.8 Hz), 7.64 (d, J = 7.8 Hz), 6.56 (d, J = 16 Hz), 2.87 (d, J = 6.68 Hz), 3.82 (S), 3.83 (S). ^{13}C NMR (CDCl$_3$, 100 MHz) δ ppm: 135.6, 109.8, 149.0, 111.2, 119.8, 128.8, 128.9, 128.5, 128.2, 129.7, 127.0, 172.3, 28.68, 55.98.

Phase 4: preparation of bis(2((E)-(3,4-dimethoxystyryl)phenyl) glutaramide) (74) (see Table 1)

To a stirred solution of the glutaryl chloride (0.030 g, 1.95 × 10^{-4} mol) and DMAP (0.052 g, 4.3 × 10^{-4} mol) in CH$_2$Cl$_2$ (4 ml) was added slowly dropwise amino stilbene (0.1 g, 3.9 × 10^{-4} mol) drop wise at 0 °C. The stirring was continued overnight and the reaction allowed to warm to room temperature. When the TLC indicated the complete consumption of starting material, the reaction mixture was extracted with ethyl acetate (2 × 30 ml) and then washed with distilled water (2 × 30 ml). The resulting organic extracts were combined and evaporated under reduced pressure to yield crude product. Purification by column chromatography (7 : 3 hexane : ethyl acetate) afforded the desired product (62% yield).

((E)-2-(3,4-Dimethoxystyryl)phenyl)glutaramide. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.92 (S), 6.83 (d, J = 8.2 Hz), 6.96 (d, J =

Table 1 ^{1}H NMR [400 Hz] and ^{13}C DEPT135, CH$_3$/CH NMR [100 Hz] in CDCl$_3$

	71 ^{1}H	71 ^{13}C	42 ^{1}H	42 ^{13}C	72 ^{1}H	72 ^{13}C	74 ^{1}H	74 ^{13}C	75 ^{1}H	75 ^{13}C
	C$_{16}$H$_{17}$NO$_2$ MW 255.32		C$_{35}$H$_{34}$N$_2$O$_6$ MW 578.67		C$_{36}$H$_{36}$N$_2$O$_6$ MW 592.69		C$_{37}$H$_{38}$N$_2$O$_6$ MW 606.72		C$_{37}$H$_{38}$N$_2$O$_5$ MW 620.75	
1	—	143.8	—	133.7	—	135.6	—	135.6	—	138.2
2	7.05 (s)	111	7.04 (S)	108.6	6.86 (S)	109.8	6.92 (S)	109.6	7.06 (S)	121.7
3	—	149.2	—	140.2	—	149.1	—	149.2	—	149.2
4	—	149	—	141.9	—	149.2	—	149.2	—	150.1
5	6.86 (d, J = 8.2 Hz)	116.2	6.69 (d, J = 8.2 Hz)	110.9	6.76 (d, J = 8.2 Hz)	111.2	6.83 (d, J = 8.2 Hz)	111.3	6.87 (d, J = 8.2 Hz)	111.3
6	7.04 (d, J = 8.2 Hz)	117.7	6.93 (d, J = 8.2 Hz)	120.5	6.92 (d, J = 8.2 Hz)	119.8	6.96 (d, J = 8.2 Hz)	121.1	7.06 (d, J = 8.2 Hz)	119.9
7	6.94 (d, J = 16 Hz)	130.2	7.05 (d, J = 16 Hz)	120.3	6.89 (d, J = 16 Hz)	121.2	6.93 (d, J = 16 Hz)	130.2	6.91 (d, J = 16 Hz)	132.5
1'	—	130.2	—	130.0	—	128.8	—	128.8	—	130.3
2'	—	130.8	—	130.0	—	128.9	—	128.9	—	133.7
3'	6.72 (d, J = 7.8 Hz)	124.1	7.52 (d, J = 7.8 Hz)	124.2	7.02 (d, J = 7.8 Hz)	128.5	7.03 (d, J = 7.7 Hz)	129.2	7.48 (d, J = 7.8 Hz)	126.9
4'	7.09 (t, J = 7.8 Hz)	128.4	7.19 (t, J = 7.8 Hz)	126.1	7.31 (t, J = 7.8 Hz)	128.2	7.32 (t, J = 7.7 Hz)	129.1	7.17 (t, J = 7.8 Hz)	125.5
5'	6.81 (t, J = 7.56 Hz)	124.2	7.23 (t, J = 7.8 Hz)	127.7	7.28 (t, J = 7.7 Hz)	129.7	7.37 (t, J = 7.7 Hz)	128.2	7.28 (t, J = 7.8 Hz)	128.1
6'	7.38 (d, J = 7.8 Hz)	127.3	7.75 (d, J = 7.8 Hz)	130.0	7.64 (d, J = 7.7 Hz)	127.1	7.68 (d, J = 7.7 Hz)	126.7	7.82 (d, J = 7.8 Hz)	124
7'	7.03 (d, J = 16 Hz)	128.6	6.84 (d, J = 16 Hz)	131.1	6.56 (d, J = 16 Hz)	132.4	6.62 (d, J = 16 Hz)	123.6	7.0 (d, J = 16 Hz)	132.5
8'	—	—	—	165.6	—	172.3	—	172.3	—	172.3
8'''	—	—	—	165.6	—	172.3	—	172.3	—	172.3
9'	—	—	3.62 (S)	44.8	2.87 (s)	28.6	2.84 (t)	33.1	2.37 (dt)	33.9
9'''	—	—	—	—	—	—	—	—	—	—
10	—	—	—	—	—	—	2.1 (m)	27.5	—	—
10'	—	—	—	—	—	—	—	—	2.42 (t)	25.1
10'''	—	—	—	—	—	—	—	—	—	—
3-Ome	3.93 (s)	55.98	3.65 (S)	55.69	3.82 (S)	55.98	3.87 (S)	55.94	3.91 (S)	55.98
4-Ome	3.90 (s)	55.93	3.84 (S)	55.87	3.83 (S)	55.98	3.90 (S)	55.98	3.94 (S)	55.99

8.2 Hz), 6.93 (d, $J = 16$ Hz), 7.03 (d, $J = 7.7$ Hz), 7.32 (t, $J = 7.7$ Hz), 7.37 (t, $J = 7.7$ Hz), 7.68 (d, $J = 7.7$ Hz), 6.62 (d, $J = 16$ Hz), 2.84 (t, $J = 6.52$ Hz), 3.87 (S), 3.90 (S), $^{13}C\{^{1}H\}$ NMR (CDCl$_3$, 100 MHz) δ 135.6, 109.6, 149.0, 149.2, 111.3, 121.1, 130.2, 128.8, 128.9, 129.17, 129.01, 129.01, 128.19, 126.74, 123.6, 172.3, 33.14, 27.5, 55.94, 55.98.

Preparation of bis(2((*E*)-(3,4-dimethoxystyryl)phenyl) adipamide) (75) (see Table 1)

To a stirred solution of adipoyl chloride (0.030 g, 1.95×10^{-4} mol) and DMAP (0.052 g, 4.3×10^{-4} mol) in CH$_2$Cl$_2$ (4 ml) was added slowly dropwise amino stilbene (0.1 g, 3.9×10^{-4} mol) at 0 °C. The stirring was continued overnight and the reaction allowed to warm to room temperature. When the TLC indicated the complete consumption of starting material, the reaction mixture was extracted with ethyl acetate (2 × 30 ml) and the washed with distilled water (2 × 30 ml). The resulting organic extracts were combined and evaporated under reduced pressure to yield crude product. Purification by column chromatography (7 : 3 hexane : ethyl acetate) afforded the desired product (63% yield).

(*E*)-2-(3,4-Dimethoxystyryl)adipamide amides. ^{1}H NMR (CDCl$_3$, 400 MHz) 7.06 (S), 6.87 (d, $J = 8.2$ Hz), 7.06 (d, $J = 8.2$ Hz), 6.91 (d, $J = 16$ Hz), 7.48 (d, $J = 7.8$ Hz), 7.17 (t, $J = 7.8$ Hz), 7.28 (t, $J = 7.8$ Hz), 7.82 (d, $J = 7.8$ Hz), 7.0 (d, $J = 16$ Hz), 2.37 (d, $J = 6.56$ Hz), 2.42 (d, $J = 84$ Hz), 3.91 (S), 3.94 (S). $^{13}C\{^{1}H\}$ NMR (CDCl$_3$, 100 MHz) δ 138.2, 121.69, 149.0, 150.0, 111.33, 119.89, 132.53, 130.3, 133.7, 126.91, 125.46, 123.98, 132.53, 172.3, 33.93, 25.17, 25.17, 55.98, 55.99.

The FeCl$_3$ promoted oxidative cascade reactions of the aminostilbene succinamide dimer (73)

Bis(2((*E*)-(3,4-dimethoxystyryl)phenyl)succinamide (0.080 g, 1.58×10^{-4} mol) was dissolved in CH$_2$Cl$_2$ (25 ml). FeCl$_3$·6H$_2$O (0.042 g, 1.58×10^{-4} mol) was added to the mixture under nitrogen. The mixture was stirred at room temperature and monitored by TLC. After the consumption of the starting malenal, saturated ammonium chloride was added to the reaction mixture followed by extracted with ethyl acetate (3 × 25 ml). The combined organic fractions were dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification of the crude product by column chromatography (7 : 3 hexane : ethyl acetate) gave rise to a major product in 61% yield.

Aminostilbene succinamide dimer (73). ^{1}H NMR (CDCl$_3$, 400 MHz) 6.94 (S), 6.40 (d, $J = 7.80$ Hz), 6.71 (d, $J = 7.80$ Hz), 7.38 (d, $J = 7.64$ Hz), 6.78 (d, $J = 7.64$ Hz), 7.15 (t, $J = 7.64$ Hz), 7.26 (t, $J = 7.64$ Hz), 6.87 (d, $J = 7.64$ Hz), 6.85 (S), 6.48 (S). $^{13}C\{^{1}H\}$ NMR (CDCl$_3$, 100 MHz) δ 176.3, 132.6, 132.44, 130.28, 129.9, 129.5, 128.6, 128.3, 127.9, 126.8, 122.0, 122.8, 112.8, 110.7, 109.9, 55.0, 55.9, 55.8, 55.9, 51.8, 49.7, 37.1, 37.1, 33.9.

Conflicts of interest

There are no conflicts to declare.

References

1 K. Ahmad, N. F. Thomas, M. R. Mukhtar, I. Noorbatcha, J.-F. F. Weber, M. A. Nafiah, S. S. Velu, K. Takeya, H. Morita and C.-G. Lim, *Tetrahedron*, 2009, **65**, 1504–1516.

2 N. F. Thomas, S. S. Velu, J.-F. F. Weber, K. Lee, A. H. A. Hadi, P. Richomme, D. Rondeau, I. Noorbatcha and K. Awang, *Tetrahedron*, 2004, **60**, 11733–11742.

3 S. P. Breazzano, Y. B. Poudel and D. L. Boger, *J. Am. Chem. Soc.*, 2013, **135**, 1600.

4 D. C. Harrowven, T. Woodcock and P. D. Howes, *Tetrahedron Lett.*, 2002, **43**, 9327–9329.

5 H. Ohno, K. Miyamura, Y. Takeoka and T. Tanaka, *Angew. Chem.*, 2003, **115**, 2751–2754.

6 J. M. Humphrey, Y. Liao, A. Ali, T. Rein, Y.-L. Wong, H.-J. Chen, A. K. Courtney and S. F. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 8584–8592.

7 K. A. Parker and Y.-H. Lim, *J. Am. Chem. Soc.*, 2004, **126**, 15968–15969.

8 P. Jones, W.-S. Li, P. Gerald and N. M. Thomson, *Tetrahedron Lett.*, 1997, **38**, 9069–9072.

9 H. Kudo, F. Sanda and T. Endo, *Tetrahedron Lett.*, 2001, **42**, 7847–7850.

10 H. Maeda, K.-i. Nishimura, K. Mizuno, M. Yamaji, J. Oshima and S. Tobita, *J. Org. Chem.*, 2005, **70**, 9693–9701.

11 H. N. Lim and K. A. Parker, *Org. Lett.*, 2012, **15**, 398–401.

12 N. L. Bauld, D. J. Bellville, R. Pabon, R. Chelsky and G. Green, *J. Am. Chem. Soc.*, 1983, **105**, 2378–2382.

13 D. J. Bellville, N. L. Bauld, R. Pabon and S. A. Gardner, *J. Am. Chem. Soc.*, 1983, **105**, 3584–3588.

14 N. A. Valley and O. Wiest, *J. Org. Chem.*, 2007, **72**, 559–566.

15 C. S. Sevov and O. Wiest, *J. Org. Chem.*, 2008, **73**, 7909–7915.

16 D. J. Bellville, D. W. Wirth and N. L. Bauld, *J. Am. Chem. Soc.*, 1981, **103**, 718–720.

17 R. A. Pabon and N. L. Bauld, *J. Am. Chem. Soc.*, 1984, **106**, 1145–1146.

18 M. Oestreich, *The Mizoroki-Heck Reaction*, John Wiley & Sons, 2009.

19 C. H. Kee, A. Ariffin, K. Awang, K. Takeya, H. Morita, S. I. Hussain, K. M. Chan, P. J. Wood, M. D. Threadgill and C. G. Lim, *Org. Biomol. Chem.*, 2010, **8**, 5646–5660.

20 C. B. Ziegler Jr and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2941–2946.

21 M. D. Forbes, *Carbon-centered free radicals and radical cations: structure, reactivity, and dynamics*, John Wiley & Sons, 2010.

22 M. S. Alehashem, C.-G. Lim and N. F. Thomas, *RSC Adv.*, 2016, **6**, 18002–18025.

23 F.-J. Hong, Y.-Y. Low, K.-W. Chong, N. F. Thomas and T.-S. Kam, *J. Org. Chem.*, 2014, **79**, 4528–4543.

24 E. Steckhan, *J. Am. Chem. Soc.*, 1978, **100**, 3526–3533.

25 K.-W. Chong, F.-J. Hong, N. F. Thomas, Y.-Y. Low and T.-S. Kam, *J. Org. Chem.*, 2017, **82**(12), 6172–6191.