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Published on Web 07/19/2005

Total Synthesis of Thiostrepton. Assembly of Key Building Blocks and Completion of the Synthesis

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Abstract: The completion of the total synthesis of thiostrepton (**1**) is described. The synthesis proceeded from key building blocks **2**−**5**, which were assembled into a growing substrate that finally led to the target molecule. Thus, the dehydropiperidine peptide core **2** was, after appropriate manipulation, coupled to the thiazoline−thiazole fragment **3**, and the resulting product was advanced to intermediate **11** possessing the thiazoline−thiazole macrocycle. The bis-dehydroalanine tail equivalent **4** and the quinaldic acid fragment **5** were then sequentially incorporated, and the products so obtained were further elaborated to forge the second macrocycle of the molecule. Several roadblocks encountered along the way were systematically investigated and overcome, finally opening the way, through intermediates **20**, **32**, **44**, **45**, and **46**, to the targeted natural product, **1**.

Introduction

In the preceding article[1] we described the retrosynthetic analysis of thiostrepton (**1**, Figure 1) and the construction of the key building blocks (**2**−**5**) required for its projected total synthesis. In this paper we discuss the assembly of these fragments and the elaboration of the resulting advanced intermediates into the final target (**1**), including a description of some of the intriguing setbacks and obstacles that we encountered, and finally overcame, en route to the destination.

Results and Discussion: Assembly of Building Blocks and Total Synthesis

According to the designed plan, our first order of business was the coupling of dehydropiperidine peptide fragment **2** with the thiazoline segment **3** and the forging of the thiazoline-containing macrocycle **11**, a task that proceeded smoothly, as summarized in Scheme 1. Thus, diastereomerically pure amine **2**[1] was converted to its *N*-Alloc derivative **6** by reaction with allyl chloroformate and *i*-Pr_2NEt in the presence of 4-DMAP as a catalyst (92% yield), and thence to *N*-Alloc 1,2-amino alcohol **7** with TFA, whose action caused collapse of both the *N*-Boc and acetonide masking devices. This amino alcohol (**7**) was then joined to thiazoline building block **3**[1] through an amide bond-forming reaction promoted by HATU, HOAt, and *i*-Pr_2-NEt, furnishing peptide bis-methyl ester **8** in 73% overall yield from *N*-Boc acetonide **6**. The next task called for regioselective hydrolysis of compound **8** to form the desired precursor (monoacid **9**) to the 26-membered thiazoline-containing macrocycle **11**, a challenge that was met only partially. Thus, under the best conditions (Me_3SnOH in 1,2-dichloroethane at 50 °C),[2] we were able to convert bis-methyl ester **8** to a ca. 2:1 mixture of monoacids (**9** + **9′**), in 52% combined yield, accompanied by 14% of the corresponding diacid and 28% of recovered starting material (**8**), both of which were, of course, recyclable. Even though the two monoacids **9** and **9′** were not separable by chromatography, nor could the major regioisomer be defined at this stage, we nevertheless pressed forward in the hope of achieving a separation at a later stage. Thus, reduction of the mixture (**9** + **9′**) with PMe_3 in the presence of H_2O at 0 °C led to the corresponding amino acids (**10** + **10′**), which were subjected to high dilution macrolactamization conditions [HATU, HOAt, *i*-Pr_2NEt, DMF (0.002 M), 25 °C, 65 h] to afford, in 32% overall yield from acids **9** and **9′**, a single macrolactam. These results indicated that one regiosomer of the amino acid (**10** or **10′**) was unable to cyclize upon activation, being instead consumed during the reaction through polymerization or decomposition pathways. Although at this juncture we were unable to definitively establish that the macrocyclic product formed in this reaction possessed the correct (and desired) regioisomeric structure, we hoped that an intrinsic preference to form macrocycle **11** existed due to its presence in the naturally occurring thiostrepton (**1**). Indeed, molecular models (manual) revealed unfavorable strain interactions for the alternative macrolactamization reaction resulting from amino acid **10′**.

(1) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, http://dx.doi.org/10.1021/ja0529337.

(2) (a) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378−1382. (b) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 355−358. (c) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A.; Pena, C.; Coba, M. P. *Tetrahedron* **1998**, *54*, 13023−13034. (d) Furlan, R. L. E.; Mascaretti, O. A. *Aldrichim. Acta* **1997**, *30*, 55−69. (e) Furlan, R. L. E.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1996**, *37*, 5229−5232.

10.1021/ja052934z CCC: $30.25

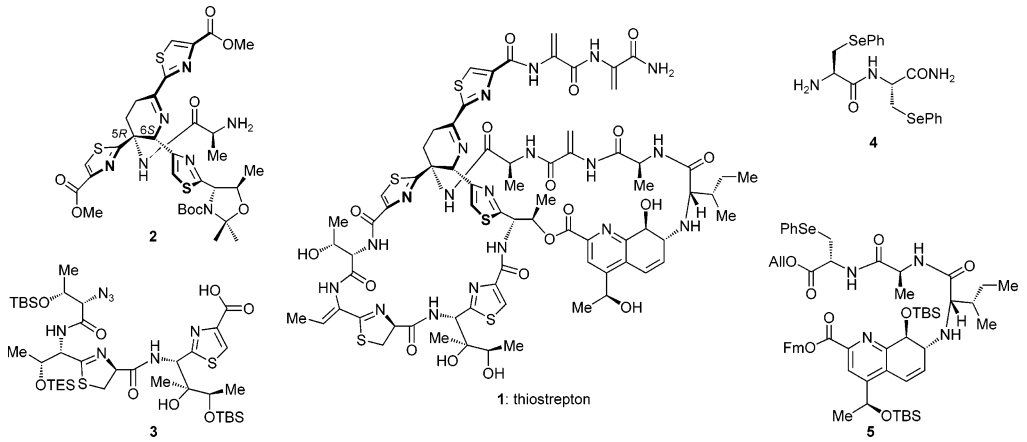
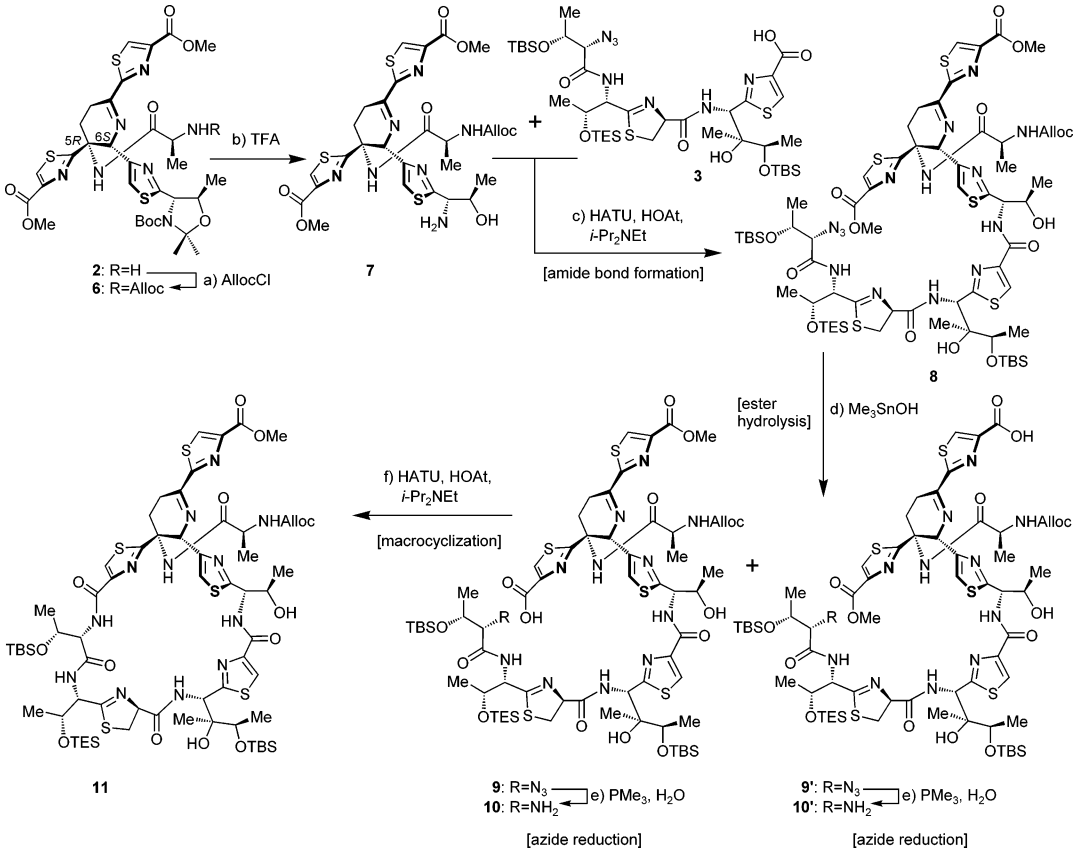


Figure 1. Thiostrepton (**1**) and key building blocks (**2**−**5**) for its total synthesis.

Scheme 1. Synthesis of Thiazoline-Containing Macrocycle **11**[a]

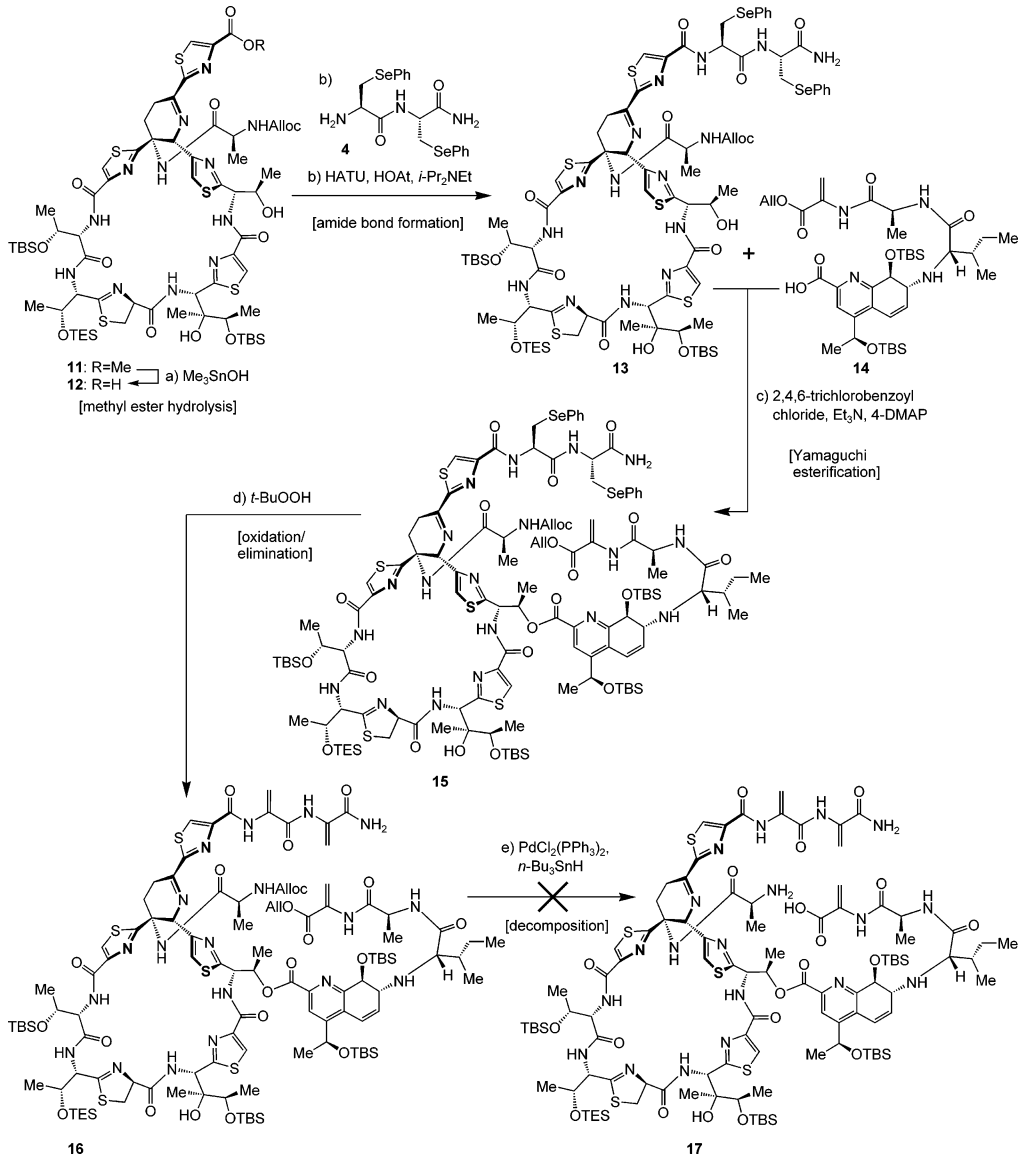


[a] Reagents and conditions: (a) AllocCl (5.0 equiv), *i*-Pr_2EtN (10 equiv), 4-DMAP (0.1 equiv), THF, 25 °C, 3 h, 92%; (b) TFA:CH_2Cl_2 (1:1), 0 °C, 10 min; then 25 °C, 45 min; (c) **7** (1.0 equiv), **3** (1.0 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), *i*-Pr_2NEt (3.0 equiv), DMF, 0 °C, 30 min, 73% (two steps); (d) Me_3SnOH (8.0 equiv), 1,2-dichloroethane, 50 °C, 4 h, 52% (plus 14% diacid and 28% recovered starting material **8**); (e) PMe_3 (6.0 equiv), THF:H_2O (10:1), 0 °C, 75 min; (f) HATU (5.0 equiv), HOAt (5.0 equiv), *i*-Pr_2NEt (6.0 equiv), DMF (0.002 M), 25 °C, 65 h, 32% (over two steps from mixture of mono acids **9** and **9′**). Abbreviations: Alloc, allyloxy carbonyl; AllocCl, allyl chloroformate; 4-DMAP, 4-dimethylaminopyridine; Boc, *tert*-butoxycarbonyl; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; DMF, *N*,*N*-dimethylformamide; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl.

Interestingly (and somewhat worrisomely), it was not until compound **11** was carried all the way through to the natural product (**1**) that this regiochemical ambiguity was resolved.

Having succeeded in forming the thiazoline macrocycle **11**, we then turned our attention to the task of attaching the bis-dehydroalanine tail as its masked equivalent **4**[1] to the growing molecule, and then proceeded with the construction of the remaining quinaldic acid-containing macrocycle (Scheme 2). Thus, in a remarkable reaction,[2] Me_3SnOH in 1,2-dichloroethane at 60 °C accomplished the quantitative hydrolysis of the methyl ester of macrocycle **11** without epimerization at any of its several potentially vulnerable stereocenters, leading to carboxylic acid **12**. The latter compound (**12**) was then coupled, through an amide bond, with bis-phenylseleno dipeptide **4**[1] by the action of HATU, HOAt, and *i*-Pr_2NEt to furnish, in 83% yield, advanced intermediate **13**. Subsequent esterification of key quinaldic acid building block **14**[1] with the branching substrate **13** using the latter compound's secondary hydroxyl group

Scheme 2. Synthesis of Advanced Seco Compound **16** and Failed Attempt To Deprotect It to Amino Acid **17**[a]



[a] Reagents and conditions: (a) Me_3SnOH (10 equiv), 1,2-dichloroethane, 60 °C, 2.5 h, 100%; (b) **4** (2.0 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), *i*-Pr_2NEt (3.0 equiv), DMF, 0 °C, 1.5 h, then 25 °C, 30 min, 83%; (c) **14** (2.0 equiv), 2,4,6-trichlorobenzoyl chloride (4.0 equiv), Et_3N (12 equiv), toluene, 25 °C, 16 h; then **13** (1.0 equiv), 4-DMAP (15 equiv), toluene, 35 min, 25 °C, 84%; (d) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (1:10), $NaHCO_3$ (30 equiv), 0 °C, 5 min; then 25 °C, 75 min, 68%; (e) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, −45 °C, 5 min; then 0 °C, 1 h. Abbreviations: All, allyl; Ph, phenyl.

proceeded admirably under modified Yamaguchi conditions[3] (2,4,6-trichlorobenzoyl chloride, Et_3N, 25 °C; then 4-DMAP, 25 °C) to give ester **15** in 84% yield. The phenylselenium moieties were then oxidatively removed from **15** by the action of *t*-BuOOH at 0−25 °C, furnishing triene **16** in 68% yield. All that now remained before the total synthesis of **1** could be declared was the removal of the *N*-Alloc and allyl ester groups guarding the amino acid ends, macroring closure, and global deprotection. That was not to be just yet, for all attempts to remove the *N*-Alloc and allyl ester groups from compound **16** (notably with the *n*-$Bu_3SnH-PdCl_2(PPh_3)$ (cat.) system)[4] failed, leading to decomposition instead.

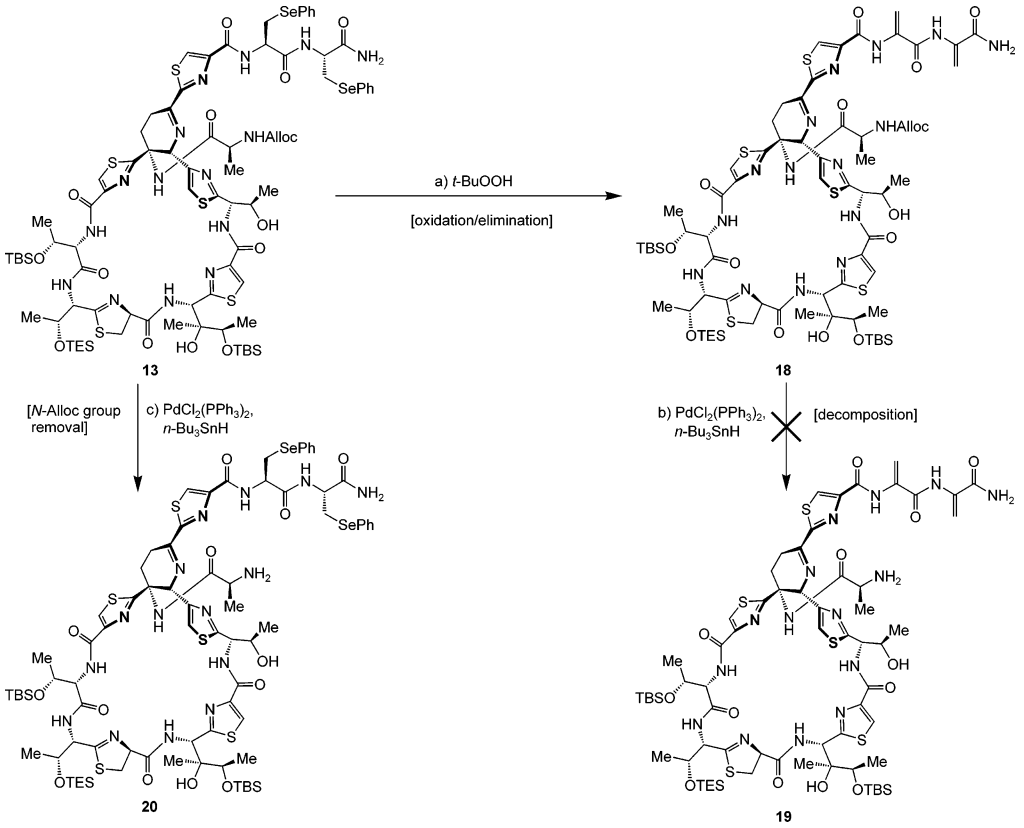
Having encountered the problem of the *N*-Alloc and ester group removal from advanced intermediate **16**, we began investigating its cause. To this end, we first exposed the bis-phenylselenium compound **13** to *t*-BuOOH, conditions that led smoothly to bis-dehydroalanine intermediate **18** in 84% yield (Scheme 3). When this dehydroalanine compound (**18**) was subjected to the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) *N*-Alloc lysis conditions, however, only decomposition was observed. Intriguingly, though, when the bis-phenylselenium precursor **13** was subjected to the same conditions, the *N*-Alloc group was cleanly removed, affording primary amine **20** in 86% yield and exposing, at the same time, the bis-dehydroalanine tail as the culprit of the earlier catastrophic attempts to achieve the desired deprotection (**16**→**17**).

At this point, and in order to gain a better understanding of the precise nature of this interference from the dehydroalanine

(3) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847−868.

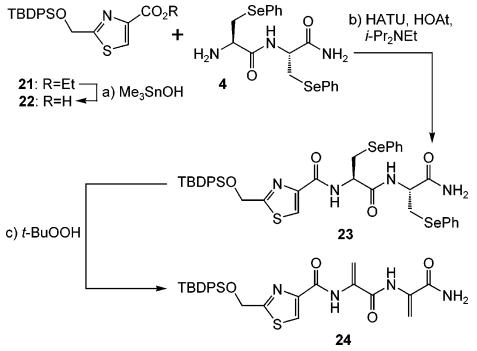
(4) (a) de la Torre, B. G.; Torres, J. L.; Bardají, E.; Clapés, P.; Xaus, N.; Jorba, X.; Calvet, S.; Albericio, F.; Valencia, G. *J. Chem. Soc., Chem. Commun.* **1990**, 965−967. (b) For a review on the use and removal of allylic protecting groups, see: Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042.

Scheme 3. *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.)-Induced *N*-Alloc Group Removal in the Presence of Phenylselenium Dehydroalanine Precursors and Failed Attempt To Remove the *N*-Alloc Group in the Presence of Dehydroalanine Residues[a]



[a] Reagents and conditions: (a) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (4:10), $NaHCO_3$ (24 equiv), 0 °C, 5 min; then 25 °C, 2 h, 84%; (b) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, −45 °C, 5 min; then 0 °C, 30 min; (c) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, −45 °C, 5 min; then 0 °C, 30 min, 86%.

Scheme 4. Synthesis of Bis-dehydroalanine Model System **24**[a]



[a] Reagents and conditions: (a) Me_3SnOH (6.0 equiv), 1,2-dichloroethane, 80 °C, 2 h, 100%; (b) amine **4** (1.0 equiv), HOAt (1.5 equiv), HATU (1.5 equiv), *i*-Pr_2NEt (3.0 equiv), DMF, 0 °C, 20 min; then 25 °C, 2 h, 85%; (c) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (6:10), 0 °C, 10 min; then 25 °C, 1.5 h, 82%. TBDPS, *tert*-butyldiphenylsilyl.

tail with the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) system, we proceeded to synthesize and study model system **24** (Scheme 4). Thus, thiazole ester **21**[5] was hydrolyzed with Me_3SnOH, furnishing carboxylic acid **22**, which was coupled with bis-phenylselenium dipeptide **4** (HATU, HOAt, *i*-Pr_2NEt) to afford compound **23** in 85% yield. Oxidation of the latter compound (**23**) with *t*-BuOOH caused the desired bis-elimination, providing bis-dehydroalanine tail system **24** in 82% yield.

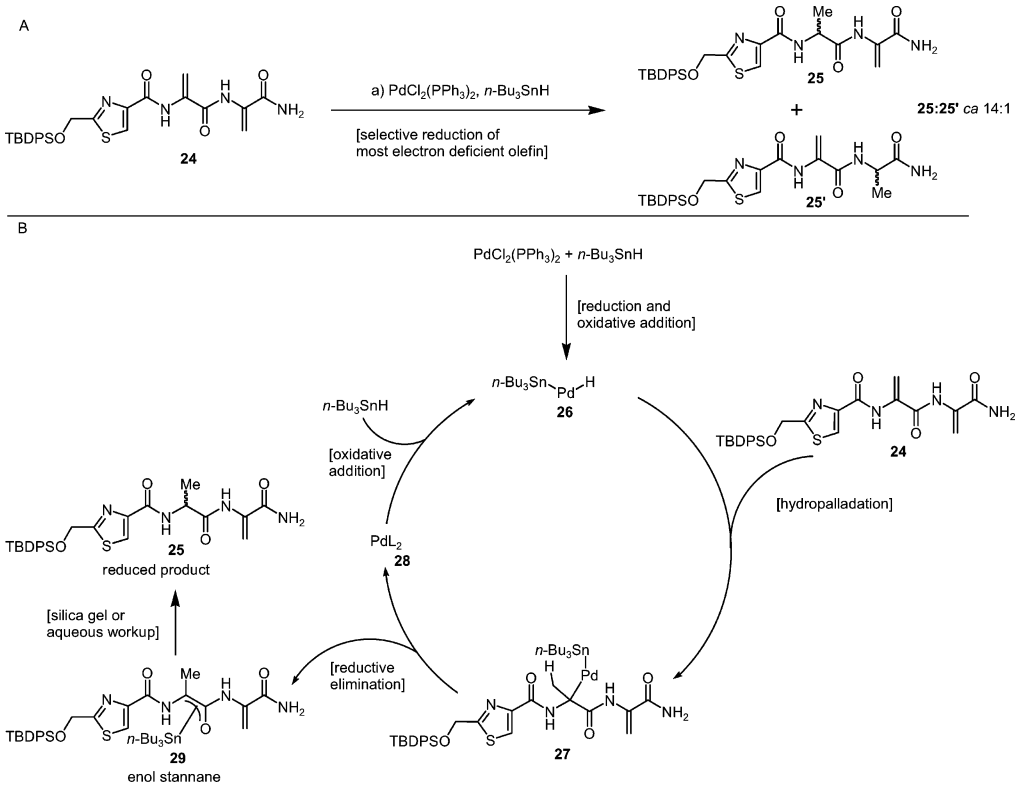
Upon exposure of model compound **24** to the *N*-Alloc removal conditions of *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.), selective reduction of the most electron-deficient (as suggested by ^1H NMR spectroscopy) olefin within **24** occurred, providing a ca. 14:1 mixture of regioisomers **25** and **25′** (Scheme 5A). These observations are reminiscent of the palladium-catalyzed 1,4-reductions of α,β-unsaturated aldehydes and ketones in which the olefins are electron-deficient.[6] Borrowing from the mechanism of these reactions, we propose, in Scheme 5B, a parallel mechanism for the observed reduction of the dehydroalanine unit. Thus, *n*-Bu_3SnH and $PdCl_2(PPh_3)_2$ are assumed to participate in a series of reduction and oxidative addition steps, producing, in situ, the active Pd(II) species **26**,[4b] which engages the olefinic substrate **24** in a hydropalladation reaction to form Pd(II)-coordinated intermediate **27**. Subsequent reductive elimination ejects enol stannane **29** and regenerates a Pd(0) species (i.e. **28**) which re-enters the catalytic cycle with its partnering reagent *n*-Bu_3SnH. Finally, exposure of enol stannane **29** to silica gel or aqueous workup conditions affords the reduced product **25**.

After failing to accomplish the liberation of the primary amino group from its Alloc-protected form within the bis-dehydroalanine intermediate **16** (Scheme 2), we proceeded to utilize the bis-phenylselenium compound **15** (Scheme 6) as the substrate for the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) deprotection step. Having previously established that both the allyl ester of the quinaldic acid substrate (**138→140**, Scheme 12 in the preceding article[1]) and the allyl carbamate of the bis-phenylselenium thiazoline

(5) Sinha, S. C.; Dutta, S.; Sun, J. *Tetrahedron Lett.* **2000**, *41*, 8243−8246.

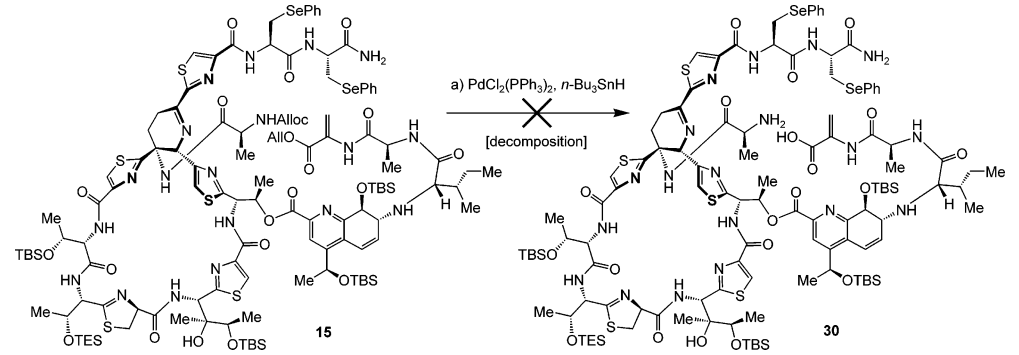
(6) (a) Keinan, E.; Gleize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477−480. (b) Four, P.; Guibé, F. *Tetrahedron Lett.* **1982**, *23*, 1825−1828.

Scheme 5. (A) Selective Reduction of Bis-dehydroalanine Model System **24** with *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.); (B) Postulated Mechanism[a]



[a] Reagents and conditions: $PdCl_2(PPh_3)_2$ (0.2 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, 0 °C, 10 min; then 25 °C, 110 min, 85%.

Scheme 6. Failed Attempt To Cleave the *N*-Alloc and Allyl Ester of Bis-phenylselenium-Containing Seco Compound **15**[a]



[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$ (0.1 equiv), *n*-Bu_3SnH (50 equiv), CH_2Cl_2, −45 °C, 5 min; then 0 °C, 30 min.

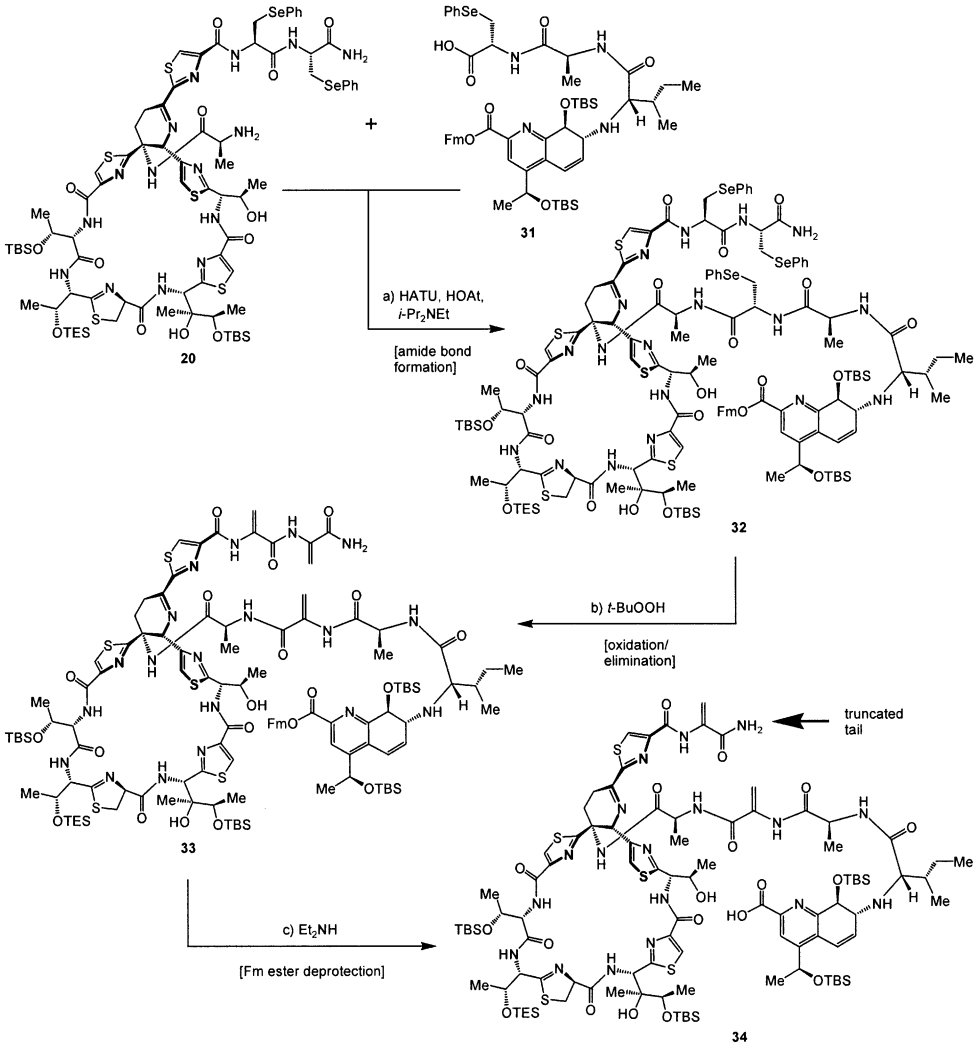
macrocycle (**13**→**20**, Scheme 3) could be efficiently dismantled by *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) without incident, we had every confidence that both protecting groups could be removed from **15** under the same conditions. Much to our dismay, however, this proved not to be the case since all our attempts to accomplish the task failed, decomposition being observed instead. This unfortunate outcome has not, as yet, been demystified and requires further investigation.

Faced with this intransigence, we opted to change the strategy for the construction of the final macrocycle. Thus, we adopted a plan which called for joining the two advanced fragments **20** and **31**[1] via an amide bond, followed by a Yamaguchi-type macrolactonization[3] (Scheme 7). This strategy variant was supported by the fact that the two fragments (**20** + **31**) independently behaved well under the conditions anticipated for their coupling and further elaboration of the resulting product. Their good behavior, however, was not to be expressed when they were in union. Thus, although both the amide bond-forming reaction between **20** and **31** (HATU, HOAt, *i*-Pr_2NEt, 68% yield) to afford **32** and the oxidative elimination of the three resident phenylselenium groups (*t*-BuOOH, 74% yield) to furnish tris-dehydroalanine derivative **33** proceeded well, the Fm ester removal step under the required basic conditions[7] failed to produce the desired product. Instead, the carboxylic acid **34**, with a truncated dehydroalanine tail, was formed in 78% yield by a seemingly mysterious but selective process.

To confirm this unexpected fragmentation, we resorted again to model system **24** (see Scheme 4 for its preparation) and, indeed, confirmed its smooth conversion to the truncated dehydroalanine compound **35** under the Fm ester removal conditions (i.e. Et_2NH),[7] as shown in Scheme 8A, and in 93% yield. Reproducible and consistent as this fragmentation process

(7) Kessler, H.; Siegmeier, R. *Tetrahedron Lett.* **1983**, *24*, 281−282.

Scheme 7. Synthesis of Advanced Intermediate **33** and Unexpected Bis-dehydroalanine Tail Cleavage under Fluorenylmethyl Ester Deprotection Conditions[a]



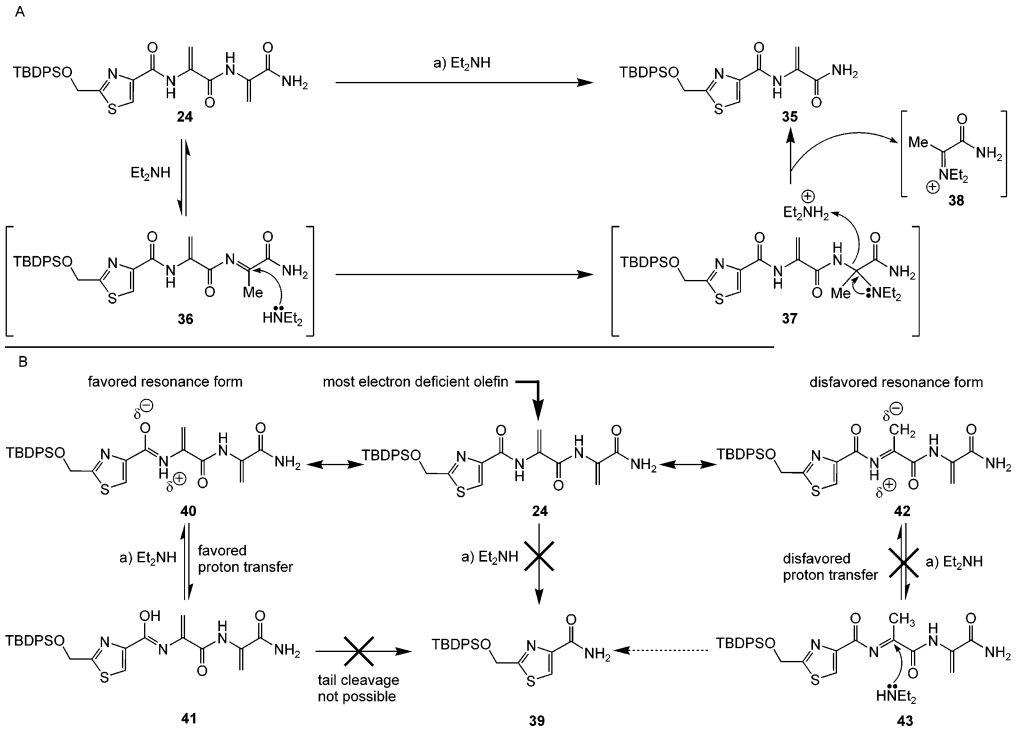
[a] Reagents and conditions: (a) **20** (1.0 equiv), **31** (1.1 equiv), HATU (1.2 equiv), HOAt (1.2 equiv), *i*-Pr_2NEt (3.0 equiv), DMF, 0 °C, 1 h, 68%; (b) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (1.2:1), 0 °C, 5 min; then 25 °C, 50 min, 74%; (c) Et_2NH:CH_2Cl_2 (1:10), 0 °C, 5 min; then 25 °C, 2.5 h, 78%. Fm, 9-fluorenylmethyl.

was, it begged for an explanation, and our proposed mechanistic rationale is shown in Scheme 8A. Thus, tautomerization of the terminal dehydroalanine unit under basic conditions to the corresponding methyl imine **36** may be followed by nucleophilic attack of Et_2NH to afford intermediate **37**, whose collapse, as shown, may form truncated dehydroalanine **35**, ejecting at the same time ionic species **38**, which is presumably hydrolyzed to the corresponding oxalate upon aqueous workup. The selectivity of this reaction is consistent with the results encountered in the *n*-$Bu_3SnH-PdCl_2(PPh_3)_2$ (cat.) interference discussed earlier (Scheme 5), whereby the internal olefin, as the most electron deficient of the two residing on the bis-dehydroalanine chain, dictates the regiochemical outcome. Thus, the mechanism shown in Scheme 8A for the cleavage of the terminal dehydroalanine moiety is presumably not operating in the case of the internal dehydroalanine unit because of the electron-withdrawing effect of the carbonyl group conjugated with the thiazole. This electron-attracting carbonyl group (more electron-withdrawing than the dehydroalanine carbonyl) could pull electron density away from the internal dehydroalanine moiety, as represented by resonance form **40** (Scheme 8B), and could, under the basic reaction conditions employed (Et_2NH), favor tautomerization to form unreactive iminol **41** at the expense of the tautomeric form poised to undergo the cleavage process (i.e. methyl imine **43**).[8]

Having stumbled once more as a result of the idiosyncrasies of the dehydroalanine units under the basic Fm ester deprotection conditions, we retreated once again back to the tris-phenylselenium precursor **32**, which pleasantly reacted smoothly in the presence of Et_2NH to afford the desired seco hydroxy carboxylic acid **44** in 87% yield (Scheme 9). This seco acid (**44**) was then subjected to the Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, Et_3N; then 4-DMAP, 25 °C), leading to the targeted compound **45**, boasting the entire ring skeleton of **1**, in 42% yield. Subsequent treatment of the latter substance (**45**) with *t*-BuOOH caused oxidative elimination of all three phenylseleno groups, generating the penta-silylated derivative **46** (68% yield) possessing all three dehydroalanine moieties, but lacking the final olefinic bond adjacent to the

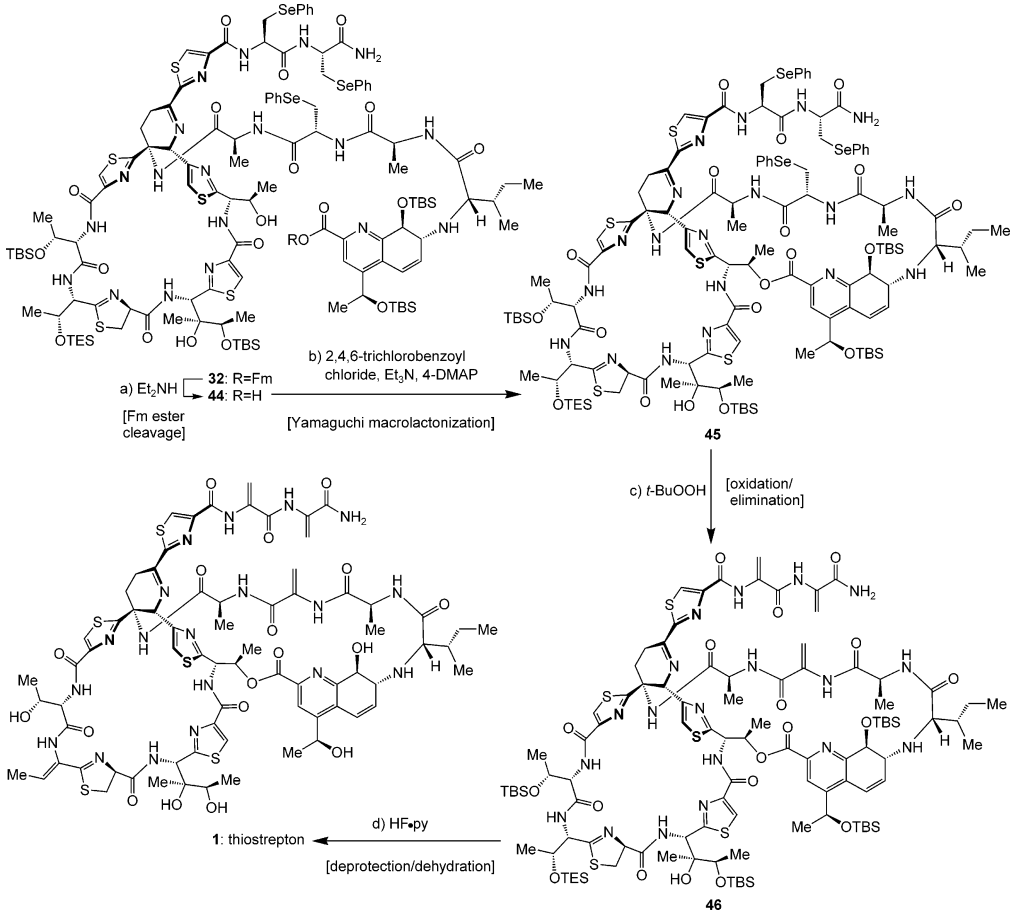
(8) For a study on the structure and chemistry of dehydroamino acids, see: Crisma, M.; Formaggio, F.; Toniolo, C.; Yoshikawa, T.; Wakamiya, T. *J. Am. Chem. Soc.* **1999**, *121*, 3272−3278.

Scheme 8. (A) Regioselective Rupture of Bis-dehydroalanine Tail Model System **24** with Et_2NH; (B) Mechanistic Rationale for the Exclusive Formation of Singly Truncated Product **35** at the Expense of Fully Truncated Product **39**[a]



[a] Reagents and conditions: (a) Et_2NH:CH_2Cl_2 (1:6.3), 0 °C, 30 min; then 25 °C, 2 h, 93%.

Scheme 9. Completion of the Total Synthesis of Thiostrepton (**1**)[a]



[a] Reagents and conditions: (a) Et_2NH:CH_2Cl_2 (1:6.5), 0 °C, 5 min; then 25 °C, 2.5 h, 87%; (b) 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), 25 °C, 24 h; then 4-DMAP (30 equiv), toluene (0.4 mM), 25 °C, 24 h, 42%; (c) *t*-BuOOH (5−6 M in decane):CH_2Cl_2 (1:5), $NaHCO_3$ (33 equiv), 0 °C, 5 min; then 25 °C, 2 h, 68%; (d) HF•py:THF (1:4), 0 °C, 5 min; then 25 °C, 24 h, 52%.

thiazoline ring. Joyfully, that final deprotection step, as successfully carried out with HF·py, not only removed all five silicon groups but was also accompanied by concomitant antiperiplanar elimination of the oxygen associated with the TES group[9] to afford the desired *Z*-trisubstituted double bond, furnishing in one fell swoop **1**. Synthetic **1** exhibited physical properties (^{1}H NMR, ^{13}C NMR, TLC, HPLC, IR, $[\alpha]^{32}_D$) identical to those of natural **1**, thus marking the end of the campaign.

Conclusion

In this and the preceding article,[1] we described our campaign to synthesize thiostrepton (**1**), one of nature's most intriguing molecules to inspire us in recent years. Lured by its unusual and complex molecular structure and interesting biological properties into the adventure, we faced several formidable challenges on the way, some reasonably predicted, some totally unexpected. One after the other, these problems were solved in a pleasing way through rational design and skillful experimentation. In the end, a body of discovery was generated from which emerged not only a successful passage from simple starting materials to **1**, but also a number of useful strategies and technologies. From the former developments, the hetero-Diels–Alder dimerization of azadienes[10] to dehydropiperidine systems stands out as a novel synthetic strategy, while from the latter category the mild hydrolysis of esters with Me_3SnOH[2] distinguishes itself as a selective and remarkably enabling method for organic synthesis. As such, the thiostrepton project fulfilled our expectations as an opportunity for discovery and invention in chemical synthesis.

Acknowledgment. We thank Drs. D. H. Huang, G. Siuzdak, and R. Chadha for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (U.S.A.), fellowships from The Academy of Finland (to M.N.), The Skaggs Institute for Research (to M.Z.), and the National Institutes of Health (to A.A.E.), and grants from Abbott, Amgen, ArrayBiopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

Supporting Information Available: Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA052934Z

(9) The stereospecific elimination of the TES-protected alcohol to provide the corresponding *Z* olefin was expected from the results of a previous model study. See Scheme 9B in the preceding article.[1]

(10) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941–1945.