ORGANIC LETTERS

2000
Vol. 2, No. 21
3317−3320

Increasing the Efficiency of the Transannular Diels–Alder Strategy via Stille Macrocyclizations

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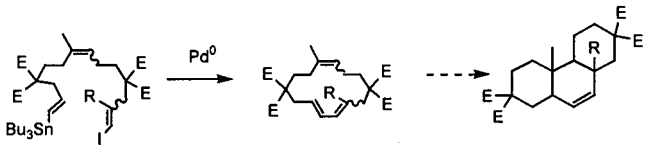
Received July 31, 2000

ABSTRACT



To increase the potential and flexibility of the transannular Diels–Alder strategy to build tricycles and tetracycles, the synthesis of macrocyclic trienes of defined geometries has been approached via Stille macrocyclization, giving very high yield and purity of the desired macrocycles or tricycles.

The Diels−Alder reaction has proven to be one of the workhorses of organic synthesis, due to its broad generality and wide applicability.[1] More than 70 years after its initial discovery, it still unveils new fundamental aspects regularly,[2] in addition to a multitude of applications. For the last few years, we have been interested in a particular application of this key reaction, namely, the transannular Diels−Alder version[3] (TADA). We have thoroughly explored the potential and limits of the TADA reaction, synthesizing a large variety of trienic macrocycles of known geometry and then studying their behavior toward the TADA transformation. It allowed for the formation of tricycles and tetracycles of well-defined stereochemistry.[4]

The bottleneck of the TADA strategy resides in the macrocyclization step, initially approached by the use of malonate connectors (dimethyl malonate, malononitrile) of low basicity (path a, Figure 1).

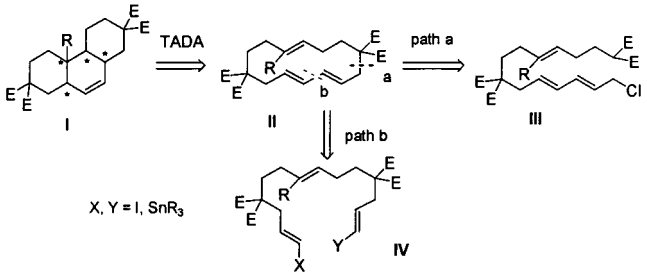


Figure 1.

These connectors allowed for the construction of a variety of macrocyclic trienes rapidly, for a systematic study of the TADA potential. However, their use as a tool for macrocyclization impedes further progress toward a total synthesis, as their subsequent transformation can be troublesome. There are a few exceptions to this rule, for example, with dimethyl

(1) For a review, see: Roush, W. R. *Adv. Cycloaddit.* **1990**, *2*, 91.
(2) Spino, C.; Pesant, M.; Dory, Y. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262.
(3) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831.
(4) For applications in total synthesis, see: (a) Toró; A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526. (b) Bélanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285. (c) Germain, J.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 4051. (d) Couturier, M.; Dory, Y. L.; Rouillard, F.; Deslongchamps, P. *Tetrahedron* **1998**, *54*, 1529. (e) Barriault, L.; Deslongchamps, P. *Bull. Soc. Chim. Fr.* **1997**, *134*, 969.

10.1021/ol000209h CCC: $19.00
Published on Web 09/22/2000

malonate which is taken advantage of in our approach to momilactone A.[4c]

In any case, to bring the TADA approach to a more flexible and efficient level in terms of synthetic strategy, we initiated a study of alternate methods of macrocyclization, the most successful ones to date making use of β-ketoester[4a,b] alkylations or ring closing metathesis,[5] which has been used for the elaboration of the dienophile part of the macrocycle.

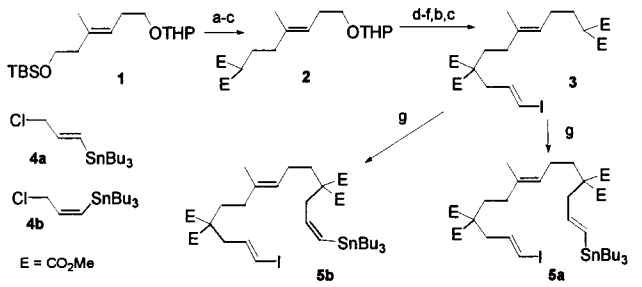
Having to systematically introduce a diene into macrocyclic trienes, with all other parts of the molecule being variable depending upon the desired target, we envisioned that the diene moiety could be formed during the macrocyclization step. This approach would completely obviate the need for a connector that would have to be subsequently elaborated. The closure of medium to large rings via Stille cross-coupling has been reported many times in the literature,[6] and it seemed that the TADA strategy would benefit from this modification (path b, Figure 1).

We are now pleased to report a study on the potential of this approach.

Malonates were selected to connect the different fragments, but this time not to effect the macrocyclization. Having been used extensively in our lab in past years, they would lead to trienic precursors via straightforward chemistry and then to known macrocycles or tricycles.

Two series of precursors were chosen, bearing respectively a *trans* or a *cis* dienophile. The synthesis of trienes **5a** and **5b** in the *trans* series from *E* precursor **1**[7] is outlined in Scheme 1.

Scheme 1

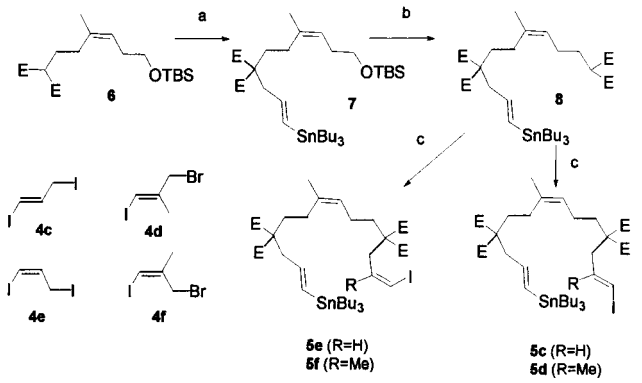


a. TBAF, THF 0°C, 2h (97%); b. MsCl, Et_3N, CH_2Cl_2 0°C, 14h (93%); c. $CH_2(CO_2Me)_2$, NaH, TBAI, THF:DMF 80°C, 14h (90%); d. NaH, **4a**, THF:DMF r.t., 14h (75%); e. I_2, CH_2Cl_2 r.t., 5 min (97%); f. *p*TSA, MeOH r.t., 5h (80%); g. NaH, **4a** or **4b**, THF:DMF, r.t. 14h (**5a**: 85%; **5b**: 64%).

After deprotection of the silyl ether, mesylation followed by malonate displacement led to malonate **2**. Subsequent alkylation followed by tin−iodine exchange led to the corresponding vinylic iodide. The THP protection was then removed, the resulting alcohol mesylated, and the mesylate further displaced with a second malonate connector to generate diene **3**. The vinylic tin residue was introduced via alkylation of the malonate moiety with allylic chlorides **4a** or **4b**[8] in order to generate acyclic trienes **5a** and **5b**, respectively, ready for Stille macrocyclization.

Synthesis of the second series possessing a *cis* dienophile followed essentially the same line of thinking, starting from dienophile **6** (available in seven steps from *m*-methylanisole)[9] as outlined in Scheme 2.

Scheme 2



a. NaH, **4a**, Bu_4NI, THF:DMF 50°C, 14h (70%); b. i: TBAF, THF, 0°C (79%); ii: MsCl, Et_3N, CH_2Cl_2, r.t, 14h (90%); iii: $CH_2(CO_2Me)_2$, NaH, Bu_4NI, THF:DMF 80°C, 14h (87%); c. NaH, 4c-4f, THF:DMF r.t., 14h (**5c**: 57%; **5d**: 59%; **5e**: 66%; **5f**: 59%).

Initial alkylation of malonate **6** with allylic chloride **4a** introduced the vinylic tin residue, which was carried out throughout the rest of the sequence. Subsequent desilylation of **7** followed by mesylation and malonate displacement furnished malonate **8** as the key precursor to trienes **5c**−**5f**. The vinylic iodide residue was introduced by alkylation of the malonate with allylic bromides or iodides **4c**−**4f**[10] to yield precursors **5c**−**5f** ready for macrocyclization. Optimization of the coupling conditions was performed on *trans-trans-trans* precursor **5a** (Table 1).

As shown in Table 1, initial attempts using Liebeskind's catalyst CuTC[11] failed to effect the desired macrocyclization (entries 1 and 2). Attention was then turned toward the classical Stille reaction, and after a few unsuccessful attempts (entries 3 and 4), we were pleased to find that acyclic TTT triene could indeed macrocyclize, in the presence of triphenylarsine as ligand and $Pd_2(dba)_3$ as the catalyst[12] to close

(5) Toró, A.; Deslongchamps, P. Manuscript in preparation.

(6) For a review, see: Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235 and references therein.

(7) Precursor **1** was synthesized in four steps from but-3-yn-1-ol with a slight modification of the method of Deslongchamps et al., see: Xu, Y.-C.; Roughton, A. L.; Plante, R.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 1152.

(8) For the synthesis of allylic chloride **4a**, see ref 4b; allylic chloride **4b** was obtained from the corresponding alcohol (Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415) by treatment with hexachloroacetone and triphenylphosphine (Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466).

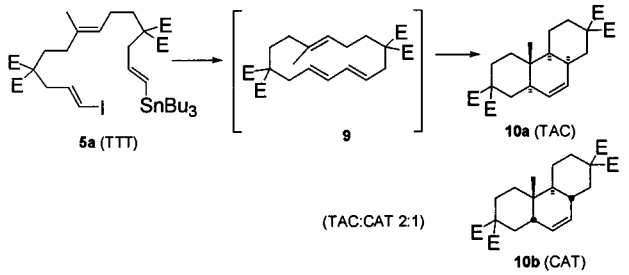
(9) Ndibwami, A.; Lamothe, S.; Guay, D.; Plante, R.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 695.

(10) For the synthesis of allylic iodides **4c** and **4e**, see ref 4a; allylic bromide **4d** was obtained from the corresponding alcohol (Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591) by bromination using the procedure given for allylic bromide **4f**. For allylic bromide **4f**, see: Larock, R. C.; Han, X. *J. Org. Chem.* **1999**, *64*, 1875.

(11) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Paterson, I.; Lombart, H.-G.; Allerton, C. *Org. Lett.* **1999**, *1*, 19.

(12) (a) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Synlett* **1995**, 267. (b) Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501. (c) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.

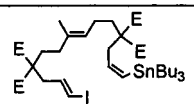
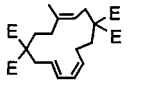
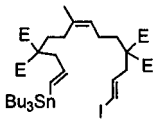
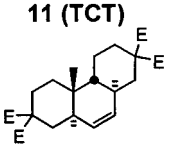
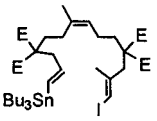
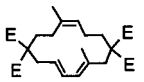
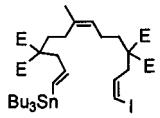
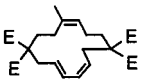
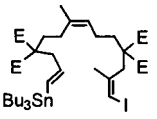
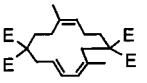
Table 1. Optimization of the Reaction Conditions



entry	catalytic system[a]	solvent	temp (°C)[b]	time (h)	products (yield, %)[c,d]
1	CuTC (3 equiv)	NMP	rt	1	none[e]
2	CuTC (10 equiv)	DMF	rt	1	none
3	$Pd_2(dba)_3$ (5%)	THF	rt	48	none
4	$Pd(MeCN)_2Cl_2$ (5%)	DMF	rt	48	none
5	$Pd_2(dba)_3$ (5%) + 0.5 equiv of $AsPh_3$	NMP	70	24	**10a**:**10b** (60)
6	$Pd_2(dba)_3$ (5%) + 0.5 equiv of $AsPh_3$ + 1 equiv of $^iPr_2NEt$	THF:DMF 1:1	70	24	**10a**:**10b** (69)
7	$Pd_2(dba)_3$ (5%) + 1 equiv of $AsPh_3$ + 1 equiv of $^iPr_2NEt$	THF:DMF 1:1	90	24	**10a**:**10b** (73)
8[f]	$Pd_2(dba)_3$ (5%) + 1 equiv of $AsPh_3$ + 1 equiv of $^iPr_2NEt$	THF:DMF 1:1	90	24	**10a**:**10b** (61)

[a] For entries 1−7, a concentration of 2 mM was used, with no slow addition. [b] Oil bath temperature. [c] Yields of isolated, pure products. [d] No trace of dimer was observed by MS. [e] Starting triene was consumed, but complex mixtures were obtained, of which no macrocycle or TADA adduct could be identified. [f] A concentration of 0.01 M was used.

Table 2. Macrocyclization of Trienes **5b**−**5f**

Entry	Triene	Products[a]	Yields (%)[b]
1	 **5b**	 **11 (TCT)**	63
2	 **5c**	 **12 (TST)**	89
3	 **5d**	 **13 ($TT^{Me}C$)**	81
4	 **5e**	 **14 (TCC)**	94
5	 **5f**	 **15 ($TC^{Me}C$)**	68

[a] All the products had spectroscopic data identical with reported values. [b] Yields of isolated, pure materials.

the diene portion of the molecule, and yield macrocycle **9** (entry 5). Under the reaction conditions, the TADA reaction occurred readily, in agreement with our previous observation[13] of the same system, to give two isomeric tricycles **10a** and **10b** having the *trans-anti-cis* and *cis-anti-trans* geometries in a ratio of 2:1 and a combined 60% yield. From our own experience, we have found the TTT macrocycles to be among the most difficult ones to close.

Adding Hünig's base to the system in order to reduce protodestannylation[14] turned out to be beneficial (entry 6), as well as increasing the quantity of triphenylarsine to 1 equiv. The optimal solvent turned out to be a 1:1 mixture of THF and DMF and the best temperature 90 °C (entry 7). Increasing the concentration from 2 to 10 mM proved detrimental to the yield (entry 8), even though no dimer was ever isolated, as could be expected.[15]

Having optimized the conditions for TTT triene, the other precursors were then tested using the best catalytic system. As reported in Table 2, the expected macrocycles or tricycles were obtained in all cases in high yields and purities using the optimized conditions. TCT macrocycle **11** (entry 1) showed the lowest yield, in agreement with the fact that during the Stille coupling the vinylic iodide moiety tolerates better steric congestion than the vinylic stannane residue.[14] In the *cis* dienophile series, TTC precursor gave directly the TST tricycle **12** in 89% yield, in agreement with previous observations[9] (entry 2). TCC macrocycle **14** proved to be the easiest to form, with an excellent 94% yield (entry 4).[16] In the TTC series, an extra methyl group on the vinylic iodide was better tolerated (entry 3) than in the TCC series (entry 5).[17] These two examples show a particularly interesting potential for the synthesis of fusidane[4e] and quassinoid[18] skeletons.

In a typical experiment, the triene (38 mg, 0.044 mmol) and triphenylarsine (13 mg, 0.044 mmol) were combined in a flask equipped with a reflux condenser. Dry THF (11 mL) and dry DMF (11 mL) were added, followed by Hünig's base (0.008 mL, 0.044 mmol). The mixture was degassed three times (vacuum then argon), then $Pd_2(dba)_3$ (2 mg, 0.0022 mmol, 5%) was added, and the mixture was degassed

(13) Ndibwami, A.; Lamothe, S.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 714.
(14) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(15) In all the experiments, no dimer was ever observed by MS analysis.
(16) Macrocycle **14** had analytical data identical to those of the previously reported product, see ref 9.
(17) Macrocycles **13** and **15** had analytical data identical to those of the reported products, see: Xu, Y.-C.; Roughton, A. L.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 1169.
(18) Barriault, L.; Ouellet, S. G.; Deslongchamps, P. *Tetrahedron* **1997**, *53*, 14937.

once more. The flask was shielded from light with aluminum foil and immersed in an oil bath at 90 °C under Ar and stirred at that temperature for 24 h. It was then cooled to rt, water (5 mL) was added, and the mixture was extracted three times with 15 mL of a 1:1 mixture of hexanes and ether. The combined organic layers were washed with brine (5 mL) and dried on magnesium sulfate, and the solvents were removed in vacuo. The macrocycle was purified by silica gel flash chromatography (ether:hexanes 10:90 to 20:80).

In essence, this series of experiments has proven the strength of the approach and has shown the Stille macrocyclizations to give equal or better results than macrocyclizations using the classical malonate alkylation.

These new results should significantly broaden the applicability of the TADA approach, as the use of connectors will now be obsolete. Applications of this key coupling in the total synthesis of natural products are now underway in our laboratory and will be reported in due course.

Acknowledgment. A basic research chair in organic chemistry from BioChem Pharma to Prof. P. Deslongchamps as well as financial support from NSERC (Canada) and from FCAR (Québec) is gratefully acknowledged. We wish to thank Mr. Laurence Dubé and Mrs. Dominique Lambert for providing allylic halides **4b** and **4e**, respectively.

Supporting Information Available: Complete characterization (^{1}H and ^{13}C NMR, IR, HRMS) as well as experimental procedures for products **2**, **3**, **5a**−**5f**, **7**, **8**, and **10**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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